(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 June 2003 (05.06.2003)

PCT

(10) International Publication Number
WO 03/045391 A1

(51) International Patent Classification⁷: A61K 31/4745, 31/4375, 31/4355, 31/4365, 31/437, 47/00, 47/26, 47/36, 47/38, 47/44, A61P 17/00, 17/02, 17/12

(21) International Application Number: PCT/US02/38190

(22) International Filing Date: 27 November 2002 (27.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/340,605 29 November 2001 (29.11.2001) US
60/378,452 6 May 2002 (06.05.2002) US

(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventors: **SKWIERCZYNSKI, Raymond, D.**; Post Office Box 33427, Saint Paul, MN 55133-3427 (US). **BUSCH, Terri, F.**; Post Office Box 33427, Saint Paul, MN 55133-3427 (US). **GUST-HEITING, Amy, L.**; Post Office Box 33427, Saint Paul, MN 55133-3427 (US). **FRETLAND, Mary, T.**; Post Office Box 33427, Saint Paul, MN 55133-3427 (US). **SCHOLZ, Matthew, T.**; Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: **ERSFELD, Dean, A.** et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

- *with international search report*

[Continued on next page]

(54) Title: PHARMACEUTICAL FORMULATIONS COMPRISING AN IMMUNE RESPONSE MODIFIER

(57) Abstract: Pharmaceutical formulations comprising an immune response modifier (IRM) chosen from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazolo-quinolineamines, oxazolo-quinolinamines, thiazolo-pyridinamines, oxazolo-pyridinamines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid are useful for the treatment of dermal associated conditions. Novel topical formulations are provided. In one embodiment, the topical formulations are advantageous for treatment of actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

WO 03/045391 A1

- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PHARMACEUTICAL FORMULATIONS COMPRISING AN IMMUNE RESPONSE MODIFIER

Field of the Invention

The present invention is directed to pharmaceutical formulations comprising at least one immune response modifier chosen from imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines. Embodiments of the present invention are directed to topical formulations for application to the skin of a mammal. Other embodiments of the present invention are directed to methods for treating dermal diseases.

Background

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, 1,2-bridged imidazoquinoline amine, thiazoloquinoline amine, oxazoloquinoline amine, thiazolopyridine amine, oxazolopyridine amine, imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, and thiazolonaphthyridine amine compounds have demonstrated potent immunostimulating, antiviral and antitumor (including anticancer) activity, and have also been shown to be useful as vaccine adjuvants. These compounds are hereinafter collectively referred to as "IRM" (immune response modifier) compounds. One of these IRM compounds, known as imiquimod, has been commercialized in a topical formulation, Aldara™, for the treatment of anogenital warts associated with human papillomavirus.

The mechanism for the antiviral and antitumor activity of these IRM compounds is thought to be due in substantial part to enhancement of the immune response by induction of various important cytokines (e.g., interferons, interleukins, tumor necrosis factor, etc.). Such compounds have been shown to stimulate a rapid release of certain monocyte/macrophage-derived cytokines and are also capable of stimulating B cells to secrete antibodies which play an important role in these IRM compounds' antiviral and antitumor activities. One of the predominant immunostimulating responses to these compounds is the induction of interferon (IFN)-α production, which is believed to be very important in the acute antiviral and antitumor activities seen. Moreover, up regulation of other cytokines such as, for example, tumor necrosis factor (TNF), Interleukin-1 (IL-1) and IL-6 also have potentially beneficial activities and are believed to contribute to the antiviral and antitumor properties of these compounds.

Although some of the beneficial effects of IRMs are known, the ability to provide therapeutic benefit via topical application of an IRM compound for treatment of a particular condition at a particular location may be hindered by a variety of factors. These factors include irritation of the skin to which the formulation is applied, formulation wash away, insolubility and/or degradation of the IRM compound in the formulation, physical instability of the formulation (e.g., separation of components, thickening, precipitation/agglomerization of active ingredient, and the like), poor permeation, and undesired systemic delivery of the topically applied IRM compound. Accordingly, there is a continuing need for new methods and formulations to provide the greatest therapeutic benefit from this class of compounds.

Summary of the Invention

At several locations throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group; it is not meant that the list is exclusive.

In one aspect, the present invention is directed to a pharmaceutical formulation comprising an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

In one embodiment, the pharmaceutical formulation comprises an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

The formulation can further comprise one or more of a preservative system, an emulsifier, and water.

In another aspect, the present invention is directed to a method of treatment of a dermal associated condition comprising applying to skin a topical formulation comprising an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

In one embodiment, the method of treatment of a dermal associated condition comprises applying to skin a formulation comprising an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

In other embodiments, the method of treatment of a dermal associated condition comprises applying to skin a formulation comprising an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and further comprising one or more of a preservative system, an emulsifier, and water.

In one embodiment, the dermal associated condition is selected from actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

In another aspect, the present invention is directed to a method for delivering an immune response modifier to a dermal surface, the method comprising the steps of selecting a formulation comprising a compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazolo-quinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers; and applying the selected formulation to the dermal surface for a time sufficient to allow the formulation to deliver the IRM to the dermal surface.

In one embodiment, the selected formulation comprises an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about”.

As used herein, “a” or “an” or “the” are used interchangeably with “at least one”, to mean “one or more” of the element being modified.

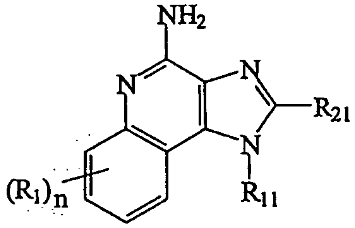
Detailed Description

In one aspect, the present invention is directed to a formulation comprising an immune response modifier compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component

miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms, and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

These immune response modifier compounds, methods of making them, methods of using them and compositions containing them are disclosed in U.S. Patent Nos. 4,689,338; 4,929,624; 4,988,815; 5,037,986; 5,175,296; 5,238,944; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,367,076; 5,389,640; 5,395,937; 5,446,153; 5,482,936; 5,693,811; 5,741,908; 5,756,747; 5,939,090; 6,039,969; 6,083,505; 6,110,929; 6,194,425; 6,245,776; 6,331,539; 6,376,669; and 6,451,810; European Patent 0 394 026; US Publication 2002/0055517; and PCT Publications WO 00/47719; WO 00/76518; WO 01/74343; WO 02/46188; WO 02/ 46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; WO 02/46194; and WO 02/46749 the disclosures of which are incorporated by reference herein.

As noted above, many of the IRM compounds useful in the present invention have demonstrated significant immunomodulating activity. In certain embodiments of the present invention, the IRM compound can be chosen from imidazoquinoline amines, for example, 1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by one of Formulas I-V below:



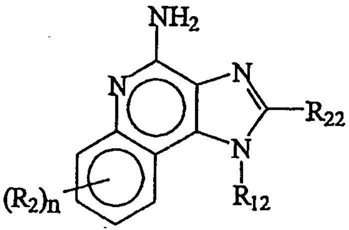
I

wherein

R_{11} is chosen from alkyl of one to ten carbon atoms, hydroxyalkyl of one to six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than six carbon atoms;

R_{21} is chosen from hydrogen, alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that when the benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms; and

each R_1 is independently chosen from alkoxy of one to four carbon atoms, halogen, and alkyl of one to four carbon atoms, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R_1 groups together contain no more than six carbon atoms;



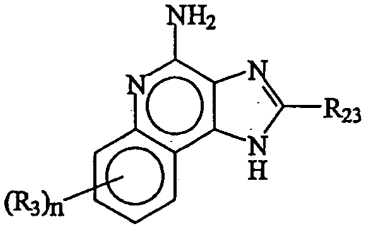
II

wherein

R_{12} is chosen from straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from straight chain or branched chain alkyl containing one to four carbon atoms and cycloalkyl containing three to six carbon atoms; and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; and

R_{22} is chosen from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from straight chain or branched chain alkyl containing one to four carbon atoms, straight chain or branched chain alkoxy containing one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each R_2 is independently chosen from straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_2 groups together contain no more than six carbon atoms;

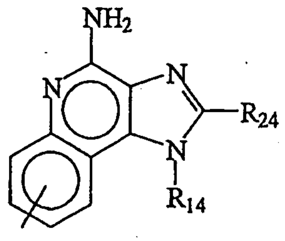


III

wherein

R_{23} is chosen from hydrogen, straight chain or branched chain alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from straight chain or branched chain alkyl of one to four carbon atoms, straight chain or branched chain alkoxy of one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each R_3 is independently chosen from straight chain or branched chain alkoxy of one to four carbon atoms, halogen, and straight chain or branched chain alkyl of one to four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_3 groups together contain no more than six carbon atoms;



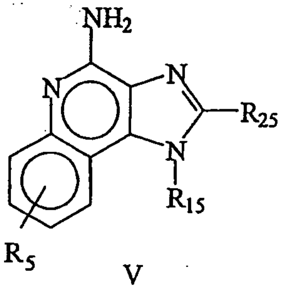
IV

wherein

R_{14} is -CHR_xR_y wherein R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently chosen from hydroxy and hydroxyalkyl of one to four carbon atoms;

R_{24} is chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen; and

R_4 is chosen from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

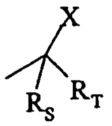


V

wherein

R_{15} is chosen from: hydrogen; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

R_{25} is



wherein

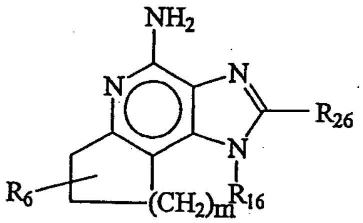
R_S and R_T are independently chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

X is chosen from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, hydroxyalkyl of one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-pyrrolidino, alkylthio of one to four carbon atoms; and

R_5 is chosen from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

and a pharmaceutically acceptable salt of any of the foregoing.

The IRM compound can also be chosen from 6,7 fused cycloalkylimidazopyridine amines defined by Formula VI below:



VI

wherein m is 1, 2, or 3;

R_{16} is chosen from hydrogen; cyclic alkyl of three, four, or five carbon atoms; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; fluoro- or chloroalkyl containing from one to ten carbon atoms and one or more fluorine or chlorine atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

and $-CHR_xR_y$

wherein

R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently chosen from hydroxy and hydroxyalkyl of one to four carbon atoms,

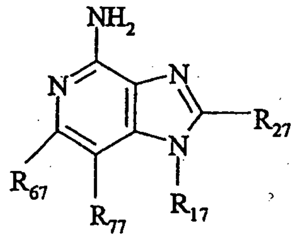
R_{26} is chosen from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, morpholinoalkyl, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety chosen from methyl, methoxy, and halogen; and

$-C(R_S)(R_T)(X)$ wherein R_S and R_T are independently chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

X is chosen from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, alkylthio of one to four carbon atoms, and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms, and

R_6 is chosen from hydrogen, fluoro, chloro, straight chain or branched chain alkyl containing one to four carbon atoms, and straight chain or branched chain fluoro- or chloroalkyl containing one to four carbon atoms and at least one fluorine or chlorine atom; and pharmaceutically acceptable salts thereof.

In other embodiments of the present invention, the IRM compound can be chosen from imidazopyridine amines defined by Formula VII below:



VII

wherein

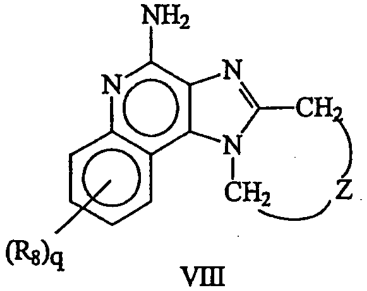
R_{17} is chosen from hydrogen; $-CH_2R_W$ wherein R_W is chosen from straight chain, branched chain, or cyclic alkyl containing one to ten carbon atoms, straight chain or branched chain alkenyl containing two to ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms, and phenylethyl; and $-CH=CR_ZR_Z$ wherein each R_Z is independently straight chain, branched chain, or cyclic alkyl of one to six carbon atoms;

R_{27} is chosen from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl oand phenyl being optionally substituted on the benzene ring by a moiety chosen from methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms;

R_{67} and R_{77} are independently chosen from hydrogen and alkyl of one to five carbon atoms, with the proviso that R_{67} and R_{77} taken together contain no more than six carbon atoms, and with the further proviso that when R_{77} is hydrogen then R_{67} is other than hydrogen and R_{27} is other than hydrogen or morpholinoalkyl, and with the further proviso that when R_{67} is hydrogen then R_{77} and R_{27} are other than hydrogen;

and pharmaceutically acceptable salts thereof.

In yet another embodiment of the present invention, the IRM compound can be chosen from 1,2-bridged imidazoquinoline amines defined by Formula VIII below:



VIII

wherein

Z is chosen from:

$-(CH_2)_p-$ wherein p is 1 to 4;

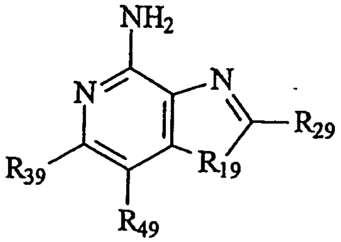
$-(CH_2)_a-C(R_DR_E)(CH_2)_b-$, wherein a and b are integers and a+b is 0 to 3, R_D is hydrogen or alkyl of one to four carbon atoms, and R_E is chosen from alkyl of one to four carbon atoms, hydroxy, $-OR_F$ wherein R_F is alkyl of one to four carbon atoms, and $-NR_GR'_G$ wherein R_G and R'_G are independently hydrogen or alkyl of one to four carbon atoms; and

$-(CH_2)_a-(Y)-(CH_2)_b-$ wherein a and b are integers and a+b is 0 to 3, and Y is O, S, or $-NR_J-$ wherein R_J is hydrogen or alkyl of one to four carbon atoms;

and wherein q is 0 or 1 and R_8 is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen,

and pharmaceutically acceptable salts thereof.

In a further embodiment, the IRM compound can be chosen from thiazoloquinoline amines, oxazoloquinoline amines, thiazolonaphthyridine amines, thiazolopyridine amines, and oxazolopyridine amines of Formula IX:



IX

wherein:

R_{19} is chosen from oxygen, sulfur and selenium;

R_{29} is chosen from

-hydrogen;
-alkyl;
-alkyl-OH;
-haloalkyl;
-alkenyl;
-alkyl-X-alkyl;
-alkyl-X-alkenyl;
-alkenyl-X-alkyl;
-alkenyl-X-alkenyl;
-alkyl-$N(R_{59})_2$;
-alkyl-N_3;
-alkyl-O-C(O)-$N(R_{59})_2$;
-heterocyclyl;
-alkyl-X-heterocyclyl;
-alkenyl-X-heterocyclyl;
-aryl;
-alkyl-X-aryl;

-alkenyl-X-aryl;
-heteroaryl;
-alkyl-X-heteroaryl; and
-alkenyl-X-heteroaryl;

R_{39} and R_{49} are each independently:

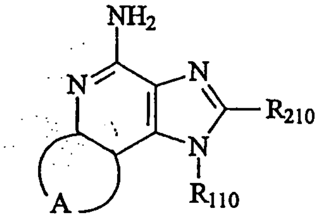
-hydrogen;
-X-alkyl;
-halo;
-haloalkyl;
-N(R_{59})$_2$;
or when taken together, R_{39} and R_{49} form a fused aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

X is chosen from –O–, –S–, –NR_{59}–, –C(O)–, –C(O)O–, –OC(O)–, and a bond; and

each R_{59} is independently H or C_{1-8}alkyl;

and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from imidazonaphthyridine amines and imidazotetrahydronaphthyridine amines of Formulae X and XI below:



X

wherein

A is =N-CR=CR-CR=; =CR-N=CR-CR=; =CR-CR=N-CR=; or =CR-CR=CR-N=;

R_{110} is chosen from:

- hydrogen;

-C_{1-20} alkyl or C_{2-20} alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -O-C_{1-20} alkyl,
- -O-(C_{1-20} alkyl)$_{0-1}$-aryl;
- -O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
- -O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
- -CO-O-C_{1-20} alkyl;
- -S(O)$_{0-2}$-C_{1-20} alkyl;
- -S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-aryl;
- -S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
- -S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
- -N(R_{310})$_2$;
- -N_3;
- oxo;
- -halogen;
- -NO_2;
- -OH; and
- -SH; and

-C_{1-20} alkyl-NR_{310}-Q-X-R_{410} or -C_{2-20} alkenyl-NR_{310}-Q-X-R_{410} wherein **Q** is –CO- or –SO_2-; **X** is a bond, -O- or -NR_{310}- and **R_{410}** is aryl; heteroaryl; heterocyclyl; or -C_{1-20} alkyl or C_{2-20} alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -O-C_{1-20} alkyl,
- -O-(C_{1-20} alkyl)$_{0-1}$-aryl;
- -O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
- -O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;

-CO-O-C_{1-20} alkyl;

-$S(O)_{0-2}$-C_{1-20} alkyl;

-$S(O)_{0-2}$-(C_{1-20} alkyl)$_{0-1}$-aryl;

-$S(O)_{0-2}$-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;

-$S(O)_{0-2}$-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;

-$N(R_{310})_2$;

-NR_{310}-CO-O-C_{1-20} alkyl;

-N_3;

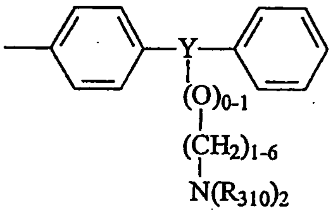
oxo;

-halogen;

-NO_2;

-OH; and

-SH; or R_{410} is



wherein Y is –N- or –CR-;

R_{210} is chosen from:

-hydrogen;

-C_{1-10} alkyl;

-C_{2-10} alkenyl;

-aryl;

-C_{1-10} alkyl -O-C_{1-10} alkyl;

-C_{1-10} alkyl-O-C_{2-10} alkenyl; and

-C_{1-10} alkyl or C_{2-10} alkenyl substituted by one or more substituents chosen from:

-OH;

-halogen;

-$N(R_{310})_2$;

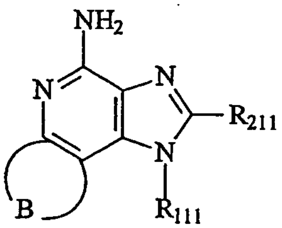
-CO-$N(R_{310})_2$;

-CO-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

each **R_{310}** is independently chosen from hydrogen and C_{1-10} alkyl; and

each **R** is independently chosen from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

and pharmaceutically acceptable salts thereof;



XI

wherein

B is -NR-C(R)$_2$-C(R)$_2$-C(R)$_2$-; -C(R)$_2$-NR-C(R)$_2$-C(R)$_2$-; -C(R)$_2$-C(R)$_2$-NR-C(R)$_2$- or -C(R)$_2$-C(R)$_2$-C(R)$_2$-NR-;

R_{111} is chosen from:

- hydrogen;

-C_{1-20} alkyl or C_{2-20} alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

-aryl;
-heteroaryl;
-heterocyclyl;
-O-C_{1-20} alkyl;
-O-(C_{1-20} alkyl)$_{0-1}$-aryl;
-O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;

-O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
-CO-O-C_{1-20} alkyl;
-S(O)$_{0-2}$ -C_{1-20} alkyl;
-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-aryl;
-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
-N(R_{311})$_2$;
-N_3;
oxo;
-halogen;
-NO_2;
-OH; and
-SH; and

-C_{1-20} alkyl-NR_{311}-Q-X-R_{411} or -C_{2-20} alkenyl-NR_{311}-Q-X-R_{411} wherein **Q** is –CO- or –SO_2-; **X** is a bond, -O- or -NR_{311}- and **R_{411}** is aryl; heteroaryl; heterocyclyl; or -C_{1-20} alkyl or C_{2-20} alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

-aryl;
-heteroaryl;
-heterocyclyl;
-O-C_{1-20} alkyl,
-O-(C_{1-20} alkyl)$_{0-1}$-aryl;
-O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
-O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
-CO-O-C_{1-20} alkyl;
-S(O)$_{0-2}$ -C_{1-20} alkyl;
-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-aryl;
-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
-N(R_{311})$_2$;
-NR_{311}-CO-O-C_{1-20} alkyl;
-N_3;

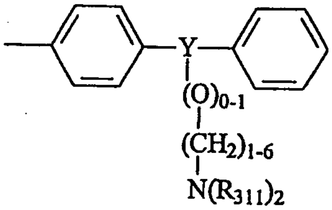
oxo;

-halogen;

-NO_2;

-OH; and

-SH; or R_{411} is



wherein **Y** is –N- or –CR-;

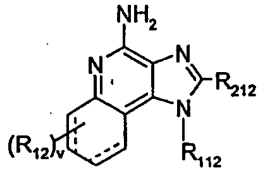
$\mathbf{R_{211}}$ is chosen from:

- -hydrogen;
- -C_{1-10} alkyl;
- -C_{2-10} alkenyl;
- -aryl
- -C_{1-10} alkyl -O-C_{1-10}-alkyl;
- -C_{1-10} alkyl-O-C_{2-10} alkenyl; and
- -C_{1-10} alkyl or C_{2-10} alkenyl substituted by one or more substituents chosen from:
  - -OH;
  - -halogen;
  - -$N(R_{311})_2$;
  - -CO-$N(R_{311})_2$;
  - -CO-C_{1-10} alkyl;
  - -N_3;
  - -aryl;
  - -heteroaryl;
  - -heterocyclyl;
  - -CO-aryl; and
  - -CO-heteroaryl;

each $\mathbf{R_{311}}$ is independently chosen from hydrogen and C_{1-10} alkyl; and each R is independently chosen from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

and pharmaceutically acceptable salts thereof.

In a further embodiment, the IRM compound can be chosen from imidazoquinoline amines and imidazotetrahydroquinoline amines, for example, 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by Formulas XII, XIII and XIV below:



XII

wherein

R_{112} is -alkyl-NR_{312}-CO-R_{412} or -alkenyl-NR_{312}-CO- R_{412} wherein **R_{412}** is aryl, heteroaryl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

-alkyl;
-alkenyl;
-alkynyl;
-$(alkyl)_{0-1}$-aryl;
-$(alkyl)_{0-1}$-(substituted aryl);
-$(alkyl)_{0-1}$-heteroaryl;
-$(alkyl)_{0-1}$-(substituted heteroaryl);
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-(substituted aryl);
-O-$(alkyl)_{0-1}$-heteroaryl;
-O-$(alkyl)_{0-1}$-(substituted heteroaryl);
-CO-aryl;
-CO-(substituted aryl);

-CO-heteroaryl;

-CO-(substituted heteroaryl);

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$ -alkyl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-(substituted aryl);

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-(substituted heteroaryl);

-$P(O)(OR_{312})_2$;

-NR_{312}-CO-O-alkyl;

-N_3;

-halogen;

-NO_2;

-CN;

-haloalkyl;

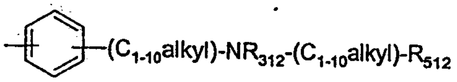
-O-haloalkyl;

-CO-haloalkyl;

-OH;

-SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

or **R_{412}** is



wherein **R_{512}** is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl), heterocyclyl or (substituted heterocyclyl) group;

R_{212} is chosen from:

-hydrogen;

-alkyl;

-alkenyl;

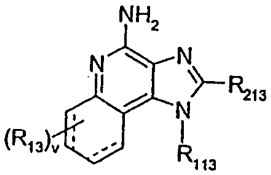
-aryl;

-(substituted aryl);
-heteroaryl;
-(substituted heteroaryl);
-heterocyclyl;
-(substituted heterocyclyl);
-alkyl -O-alkyl;
-alkyl-O-alkenyl; and
-alkyl or alkenyl substituted by one or more substituents chosen from:
  -OH;
  -halogen;
  -N(R_{312})$_2$;
  -CO-N(R_{312})$_2$;
  -CO-C_{1-10} alkyl;
  -CO-O-C_{1-10} alkyl;
  -N_3;
  -aryl;
  -(substituted aryl);
  -heteroaryl;
  -(substituted heteroaryl);
  -heterocyclyl;
  -(substituted heterocyclyl);
  -CO-aryl; and
  -CO-heteroaryl;

each **R_{312}** is independently chosen from hydrogen; C_{1-10} alkyl-heteroaryl; C_{1-10} alkyl-(substituted heteroaryl); C_{1-10} alkyl–aryl; C_{1-10} alkyl–(substituted aryl) and C_{1-10} alkyl;

v is 0 to 4;

and each **R_{12}** present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl;



XIII

wherein

R_{113} is -alkyl-NR_{313}- SO_2 -X-R_{413} or -alkenyl-NR_{313}- SO_2 –X-R_{413} ;

X is a bond or –NR_{513}-;

R_{413} is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)$_{0-1}$-aryl;

-O-(alkyl)$_{0-1}$-substituted aryl;

-O-(alkyl)$_{0-1}$-heteroaryl;

-O-(alkyl)$_{0-1}$-substituted heteroaryl;

-O-(alkyl)$_{0-1}$-heterocyclyl;

-O-(alkyl)$_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)$_{0-2}$ -alkyl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-aryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-substituted aryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heteroaryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-substituted heteroaryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heterocyclyl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-substituted heterocyclyl;
-$(alkyl)_{0-1}$-$NR_{313}R_{313}$;
-$(alkyl)_{0-1}$-NR_{313}-CO-O-alkyl;
-$(alkyl)_{0-1}$-NR_{313}-CO-alkyl;
-$(alkyl)_{0-1}$-NR_{313}-CO-aryl;
-$(alkyl)_{0-1}$-NR_{313}-CO-substituted aryl;
-$(alkyl)_{0-1}$-NR_{313}-CO-heteroaryl;
-$(alkyl)_{0-1}$-NR_{313}-CO-substituted heteroaryl;
-N_3;
-halogen;
-haloalkyl;
-haloalkoxy;
-CO-haloalkyl;
-CO-haloalkoxy;
-NO_2;
-CN;
-OH;
-SH; and in the case that R_{413} is alkyl, alkenyl, or heterocyclyl, oxo;

R_{213} is chosen from:
-hydrogen;
-alkyl;
-alkenyl;
-aryl;
-substituted aryl;
-heteroaryl;
-substituted heteroaryl;
- alkyl-O-alkyl;
- alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

-OH;

-halogen;

-N(R_{313})$_2$;

-CO-N(R_{313})$_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

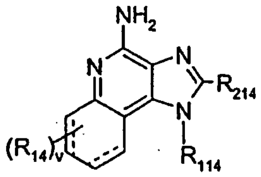
-CO-heteroaryl; and

-CO-(substituted heteroaryl);

each **R_{313}** is independently chosen from hydrogen, C_{1-10} alkyl, and when X is a bond **R_{313}** and **R_{413}** can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

R_{513} is chosen from hydrogen, C_{1-10} alkyl, and **R_{413}** and **R_{513}** can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4 and each **R_{13}** present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl;



XIV

wherein

R$_{114}$ is -alkyl-NR$_{314}$-CY-NR$_{514}$-X-R$_{414}$ or -alkenyl-NR$_{314}$-CY- NR$_{514}$-X- R$_{414}$ wherein

Y is =O or =S;

X is a bond, -CO- or –SO$_2$-;

R$_{414}$ is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-(alkyl)$_{0-1}$-aryl;
-O-(alkyl)$_{0-1}$-substituted aryl;
-O-(alkyl)$_{0-1}$-heteroaryl;
-O-(alkyl)$_{0-1}$-substituted heteroaryl;
-O-(alkyl)$_{0-1}$-heterocyclyl;
-O-(alkyl)$_{0-1}$-substituted heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;

-$S(O)_{0-2}$-alkyl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-aryl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-substituted aryl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-heteroaryl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-substituted heteroaryl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-heterocyclyl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-substituted heterocyclyl;

-(alkyl)$_{0-1}$-$NR_{314}R_{314}$;

-(alkyl)$_{0-1}$-NR_{314}-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_{314}-CO-alkyl;

-(alkyl)$_{0-1}$-NR_{314}-CO-aryl;

-(alkyl)$_{0-1}$-NR_{314}-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR_{314}-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_{314}-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and, in the case that R_{414} is alkyl, alkenyl or heterocyclyl, oxo;

with the proviso that when X is a bond R_{414} can additionally be hydrogen;

R_{214} is chosen from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl -O-alkyl;
- alkyl-O- alkenyl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:
  - -OH;
  - -halogen;
  - $-N(R_{314})_2$;
  - $-CO-N(R_{314})_2$;
  - $-CO-C_{1-10}$ alkyl;
  - $-CO-O-C_{1-10}$ alkyl;
  - $-N_3$;
  - -aryl;
  - -substituted aryl;
  - -heteroaryl;
  - -substituted heteroaryl;
  - -heterocyclyl;
  - -substituted heterocyclyl;
  - -CO-aryl;
  - -CO-(substituted aryl);
  - -CO-heteroaryl; and
  - -CO-(substituted heteroaryl);

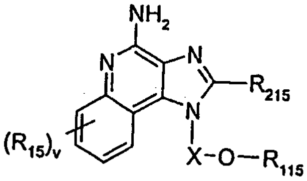
each $\mathbf{R_{314}}$ is independently chosen from hydrogen and C_{1-10} alkyl;

$\mathbf{R_{514}}$ is chosen from hydrogen, C_{1-10} alkyl, and $\mathbf{R_{414}}$ and $\mathbf{R_{514}}$ can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4 and each $\mathbf{R_{14}}$ present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

and pharmaceutically acceptable salts thereof.

In yet another embodiment, the IRM compound can be chosen from imidazoquinoline amines and imidazotetrahydroquinoline amines, for example, 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro- 1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by Formulas XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, and XXVI below



XV

wherein: **X** is $-CHR_{515}-$, $-CHR_{515}$-alkyl-, or $-CHR_{515}$-alkenyl-;

R$_{115}$ is chosen from:

- $-R_{415}-CR_{315}-Z-R_{615}-$alkyl;
- $-R_{415}-CR_{315}-Z-R_{615}-$alkenyl;
- $-R_{415}-CR_{315}-Z-R_{615}-$aryl;
- $-R_{415}-CR_{315}-Z-R_{615}-$heteroaryl;
- $-R_{415}-CR_{315}-Z-R_{615}-$heterocyclyl;
- $-R_{415}-CR_{315}-Z-H$;
- $-R_{415}-NR_{715}-CR_{315}-R_{615}-$alkyl;
- $-R_{415}-NR_{715}-CR_{315}-R_{615}-$alkenyl;
- $-R_{415}-NR_{715}-CR_{315}-R_{615}-$aryl;
- $-R_{415}-NR_{715}-CR_{315}-R_{615}-$heteroaryl;
- $-R_{415}-NR_{715}-CR_{315}-R_{615}-$heterocyclyl; and
- $-R_{415}-NR_{715}-CR_{315}-R_{815}$;

Z is $-NR_{515}-$, $-O-$, or $-S-$;

R$_{215}$ is chosen from:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -alkyl-Y-alkyl;
- -alkyl-Y- alkenyl;
- -alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
    - -OH;
    - -halogen;
    - $-N(R_{515})_2$;
    - $-CO-N(R_{515})_2$;
    - $-CO-C_{1-10}$ alkyl;
    - $-CO-O-C_{1-10}$ alkyl;
    - $-N_3$;
    - -aryl;
    - -heteroaryl;
    - -heterocyclyl;
    - -CO-aryl; and
    - -CO-heteroaryl;

$\mathbf{R_{315}}$ is =O or =S;

$\mathbf{R_{415}}$ is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each $\mathbf{R_{515}}$ is independently H or C_{1-10} alkyl;

$\mathbf{R_{615}}$ is a bond, alkyl, or alkenyl, which may be interrupted by one or more –O– groups;

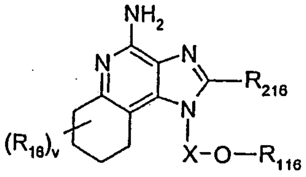
$\mathbf{R_{715}}$ is H, C_{1-10} alkyl, arylalkyl, or R_{415} and R_{715} can join together to form a 5 to 7 membered heterocylcic ring;

$\mathbf{R_{815}}$ is H, C_{1-10} alkyl, or R_{715} and R_{815} can join together to form a 5 to 7 membered heterocyclic ring;

Y is –O– or $-S(O)_{0-2}-$;

v is 0 to 4; and

each $\mathbf{R_{15}}$ present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XVI

wherein: X is $-CHR_{516}-$, $-CHR_{516}$-alkyl-, or $-CHR_{516}$-alkenyl-;

R_{116} is chosen from:

- $-R_{416}-CR_{316}-Z-R_{616}$—alkyl;
- $-R_{416}-CR_{316}-Z-R_{616}$—alkenyl;
- $-R_{416}-CR_{316}-Z-R_{616}$—aryl;
- $-R_{416}-CR_{316}-Z-R_{616}$—heteroaryl;
- $-R_{416}-CR_{316}-Z-R_{616}$—heterocyclyl;
- $-R_{416}-CR_{316}-Z-H$;
- $-R_{416}-NR_{716}-CR_{316}-R_{616}$—alkyl;
- $-R_{416}-NR_{716}-CR_{316}-R_{616}$—alkenyl;
- $-R_{416}-NR_{716}-CR_{316}-R_{616}$–aryl;
- $-R_{416}-NR_{716}-CR_{316}-R_{616}$–heteroaryl;
- $-R_{416}-NR_{716}-CR_{316}-R_{616}$–heterocyclyl; and
- $-R_{416}-NR_{716}-CR_{316}-R_{816}$;

Z is $-NR_{516}-$, –O–, or –S–;

R_{216} is chosen from:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -alkyl-Y-alkyl;
- -alkyl-Y- alkenyl;
- -alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

  - -OH;
  - -halogen;
  - $-N(R_{516})_2$;
  - $-CO-N(R_{516})_2$;
  - $-CO-C_{1-10}$ alkyl;
  - $-CO-O-C_{1-10}$ alkyl;
  - $-N_3$;
  - -aryl;
  - -heteroaryl;
  - -heterocyclyl;
  - -CO-aryl; and
  - -CO-heteroaryl;

R_{316} is =O or =S;

R_{416} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each **R_{516}** is independently H or C_{1-10} alkyl;

R_{616} is a bond, alkyl, or alkenyl, which may be interrupted by one or more –O– groups;

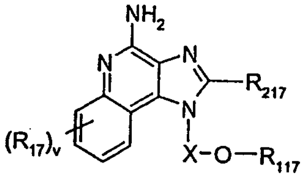
R_{716} is H, C_{1-10} alkyl, arylalkyl, or R_{416} and R_{716} can join together to form a 5 to 7 membered hetercyclic ring;

R_{816} is H or C_{1-10} alkyl; or R_{716} and R_{816} can join together to form a 5 to 7 membered heterocyclic ring;

Y is –O– or $-S(O)_{0-2}-$;

v is 0 to 4; and

each **R_{16}** present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen, and trifluoromethyl;



XVII

wherein: X is –CHR_{317}-, -CHR_{317}-alkyl-, or –CHR_{317}-alkenyl-;

R_{117} is chosen from:

- -alkenyl;
- -aryl; and
- -R_{417}–aryl;

R_{217} is chosen from:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -alkyl-Y-alkyl;
- -alkyl-Y- alkenyl;
- -alkyl-Y-aryl; and
- - alkyl or alkenyl substituted by one or more substituents chosen from:
  - -OH;
  - -halogen;
  - -$N(R_{317})_2$;
  - -CO-$N(R_{317})_2$;
  - -CO-C_{1-10} alkyl;
  - -CO-O-C_{1-10} alkyl;
  - -N_3;
  - -aryl;
  - -heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

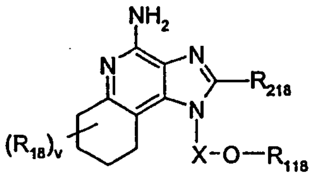
R_{417} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each R_{317} is independently H or C_{1-10} alkyl;

each Y is independently –O– or $-S(O)_{0-2}-$;

v is 0 to 4; and

each R_{17} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XVIII

wherein: X is $-CHR_{318}-$, $-CHR_{318}$-alkyl-, or $-CHR_{318}$-alkenyl-;

R_{118} is chosen from:

-aryl;

-alkenyl; and

$-R_{418}$–aryl;

R_{218} is chosen from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y-aryl;

- alkyl-Y- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

-OH;

-halogen;

-N(R_{318})$_2$;

-CO-N(R_{318})$_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

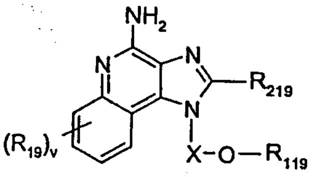
R_{418} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each **R_{318}** is independently H or C_{1-10} alkyl;

each **Y** is independently –O– or –S(O)$_{0-2}$-;

v is 0 to 4; and

each **R_{18}** present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XIX

wherein: **X** is –CHR$_{319}$-, -CHR$_{319}$-alkyl-, or –CHR$_{319}$-alkenyl-;

R_{119} is chosen from:

-heteroaryl;

-heterocyclyl;

-R_{419}– heteroaryl; and

-R_{419}–heterocyclyl;

R_{219} is chosen from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

  -OH;

  -halogen;

  -$N(R_{319})_2$;

  -CO-$N(R_{319})_2$;

  -CO-C_{1-10} alkyl;

  -CO-O-C_{1-10} alkyl;

  -N_3;

  -aryl;

  -heteroaryl;

  -heterocyclyl;

  -CO-aryl; and

  -CO-heteroaryl;

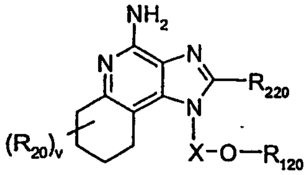
R_{419} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each **R_{319}** is independently H or C_{1-10} alkyl;

each **Y** is independently –O– or –$S(O)_{0-2}$-;

v is 0 to 4; and

each R_{19} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XX

wherein: **X** is $-CHR_{320}-$, $-CHR_{320}$-alkyl-, or $-CHR_{320}$-alkenyl-;

R_{120} is chosen from:

-heteroaryl;

-heterocyclyl;

$-R_{420}-$ heteroaryl; and

$-R_{420}-$heterocyclyl;

R_{220} is chosen from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

-OH;

-halogen;

$-N(R_{320})_2$;

$-CO-N(R_{320})_2$;

$-CO-C_{1-10}$ alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

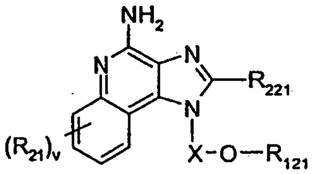
R_{420} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each **R_{320}** is independently H or C_{1-10} alkyl;

each **Y** is independently –O– or –S(O)$_{0-2}$-;

v is 0 to 4; and

each **R_{20}** present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XXI

wherein: **X** is –CHR$_{521}$-, -CHR$_{521}$-alkyl-, or –CHR$_{521}$-alkenyl-;

R_{121} is chosen from:

-R_{421}—NR_{321}—SO_2—R_{621}—alkyl;

-R_{421}—NR_{321}—SO_2—R_{621}—alkenyl;

-R_{421}–NR_{321}–SO_2–R_{621}–aryl;

-R_{421}–NR_{321}–SO_2–R_{621}–heteroaryl;

-R_{421}–NR_{321}–SO_2–R_{621}–heterocyclyl;

-R_{421}—NR_{321}—SO_2—R_{721};

-R_{421}-NR_{321}-SO_2-NR_{521}-R_{621}-alkyl;

-R_{421}-NR_{321}-SO_2-NR_{521}-R_{621}-alkenyl;

-R_{421}-NR_{321}-SO_2-NR_{521}-R_{621}-aryl;

-R_{421}-NR_{321}-SO_2-NR_{521}-R_{621}-heteroaryl;
-R_{421}-NR_{321}-SO_2-NR_{521}-R_{621}-heterocyclyl; and
-R_{421}-NR_{321}-SO_2-NH_2;

R_{221} is chosen from:

-hydrogen;
-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-alkyl-Y-alkyl;
-alkyl-Y- alkenyl;
-alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:

-OH;
-halogen;
-$N(R_{521})_2$;
-CO-$N(R_{521})_2$;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

Y is -O- or -$S(O)_{0-2}$-;

R_{321} is H, C_{1-10} alkyl, or arylalkyl;

each **R_{421}** is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups, or R_{321} and R_{421} can join together to form a 5 to 7 membered heterocyclic ring;

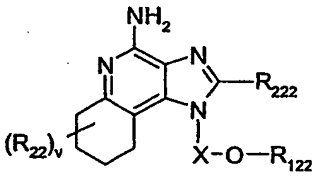
each R_{521} is independently H, C_{1-10} alkyl, or C_{2-10} alkenyl;

R_{621} is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R_{721} is C_{1-10} alkyl, or R_{321} and R_{721} can join together to form a 5 to 7 membered heterocyclic ring;

v is 0 to 4; and

each R_{21} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XXII

wherein: X is $-CHR_{522}$-, $-CHR_{522}$-alkyl-, or $-CHR_{522}$-alkenyl-;

R_{122} is chosen from:

- $-R_{422}-NR_{322}-SO_2-R_{622}-$alkyl;
- $-R_{422}-NR_{322}-SO_2-R_{622}-$alkenyl;
- $-R_{422}-NR_{322}-SO_2-R_{622}-$aryl;
- $-R_{422}-NR_{322}-SO_2-R_{622}-$heteroaryl;
- $-R_{422}-NR_{322}-SO_2-R_{622}-$heterocyclyl;
- $-R_{422}-NR_{322}-SO_2-R_{722}$;
- $-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-$alkyl;
- $-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-$alkenyl;
- $-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-$aryl;
- $-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-$heteroaryl;
- $-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-$heterocyclyl; and
- $-R_{422}-NR_{322}-SO_2-NH_2$;

R_{222} is chosen from:

- -hydrogen;
- -alkyl;

-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-alkyl-Y-alkyl;
-alkyl-Y- alkenyl;
-alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents chosen from:
    -OH;
    -halogen;
    -N(R_{522})$_2$;
    -CO-N(R_{522})$_2$;
    -CO-C_{1-10} alkyl;
    -CO-O-C_{1-10} alkyl;
    -N_3;
    -aryl;
    -heteroaryl;
    -heterocyclyl;
    -CO-aryl; and
    -CO-heteroaryl;

Y is -O- or -S(O)$_{0-2}$-;

R_{322} is H, C_{1-10} alkyl, or arylalkyl;

each **R_{422}** is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups, or R_{322} and R_{422} can join together to form a 5 to 7 membered heterocyclic ring;

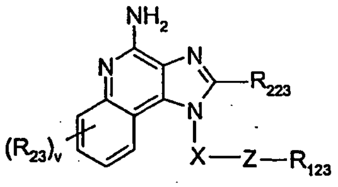
each **R_{522}** is independently H, C_{1-10} alkyl, or C_{2-10} alkenyl;

R_{622} is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R_{722} is C_{1-10} alkyl, or R_{322} and R_{722} can join together to form a 5 to 7 membered heterocyclic ring;

v is 0 to 4; and

each R_{22} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen, and trifluoromethyl;



XXIII

wherein: **X** is –CHR_{323}-, -CHR_{323}-alkyl-, or –CHR_{323}-alkenyl-;

Z is –S-, -SO-, or-SO_2-;

R_{123} is chosen from:

-alkyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkenyl;

-R_{423}–aryl;

-R_{423}– heteroaryl;

-R_{423}–heterocyclyl;

R_{223} is chosen from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

- alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

-OH;

-halogen;

-N(R_{323})$_2$;

-CO-N(R_{323})$_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

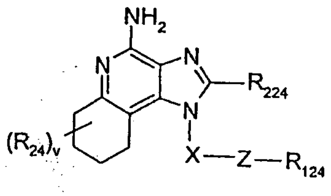
each **R_{323}** is independently H or C_{1-10} alkyl;

each **R_{423}** is independently alkyl or alkenyl;

each **Y** is independently –O– or –S(O)$_{0-2}$-;

v is 0 to 4; and

each **R_{23}** present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XXIV

wherein: **X** is –CHR$_{324}$-, -CHR$_{324}$-alkyl-, or –CHR$_{324}$-alkenyl-;

Z is –S-, -SO-, or –SO$_2$-;

R_{124} is chosen from:

-alkyl;

-aryl;

-heteroaryl;

-heterocyclyl;

- -alkenyl;
- -R_{424}–aryl;
- -R_{424}– heteroaryl; and
- -R_{424}–heterocyclyl;

R_{224} is chosen from:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -alkyl-Y-alkyl;
- - alkyl-Y- alkenyl;
- -alkyl-Y-aryl; and
- - alkyl or alkenyl substituted by one or more substituent chosen from:
  - -OH;
  - -halogen;
  - -N(R_{324})$_2$;
  - -CO-N(R_{324})$_2$;
  - -CO-C_{1-10} alkyl;
  - -CO-O-C_{1-10} alkyl;
  - -N_3;
  - -aryl;
  - -heteroaryl;
  - -heterocyclyl;
  - -CO-aryl; and
  - -CO-heteroaryl;

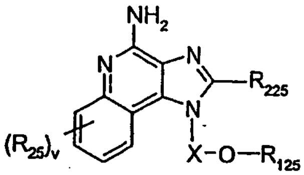
each R_{324} is independently H or C_{1-10} alkyl;

each R_{424} is independently alkyl or alkenyl;

each Y is independently –O– or –S(O)$_{0-2}$-;

v is 0 to 4; and

each R_{24} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XXV

wherein: X is $-CHR_{525}-$, $-CHR_{525}$-alkyl-, or $-CHR_{525}$-alkenyl-;

R_{125} is chosen from:

- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-$alkyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-$alkenyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-$aryl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-$heteroaryl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}-$heterocyclyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}R_{725}$;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-$alkyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-$alkenyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-$aryl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-$heteroaryl; and
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}-$heterocyclyl;

R_{225} is chosen from:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -alkyl-Y-alkyl;
- -alkyl-Y- alkenyl;
- -alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents chosen from:

    -OH;
    -halogen;
    -N(R_{525})$_2$;
    -CO-N(R_{525})$_2$;
    -CO-C_{1-10} alkyl;
    -CO-O-C_{1-10} alkyl;
    -N_3;
    -aryl;
    -heteroaryl;
    -heterocyclyl;
    -CO-aryl; and
    -CO-heteroaryl;

each **R_{325}** is =O or =S;

each **R_{425}** is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each **R_{525}** is independently H or C_{1-10} alkyl;

R_{625} is a bond, alkyl, or alkenyl, which may be interrupted by one or more –O– groups;

R_{725} is H, C_{1-10} alkyl which may be interrupted by a hetero atom, or R_{725} can join with R_{525} to form a 5 to 7 membered heterocyclic ring;

R_{825} is H, C_{1-10} alkyl, arylalkyl, or R_{425} and R_{825} can join together to form a 5 to 7 membered heterocyclic ring;

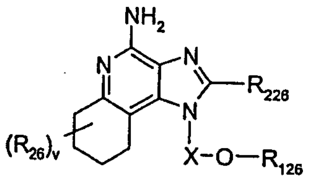
R_{925} is C_{1-10} alkyl which can join together with R_{825} to form a 5 to 7 membered heterocyclic ring;

each **Y** is independently –O– or –S(O)$_{0-2}$–;

Z is a bond, –CO–, or –SO_2–;

v is 0 to 4; and

each **R_{25}** present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl;



XXVI

wherein: X is $-\mathrm{CHR}_{526}-$, $-\mathrm{CHR}_{526}-$alkyl-, or $-\mathrm{CHR}_{526}-$alkenyl-;

R$_{126}$ is chosen from:

- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{526}-\mathrm{Z}-\mathrm{R}_{626}-$alkyl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{526}-\mathrm{Z}-\mathrm{R}_{626}-$alkenyl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{526}-\mathrm{Z}-\mathrm{R}_{626}-$aryl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{526}-\mathrm{Z}-\mathrm{R}_{626}-$heteroaryl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{526}-\mathrm{Z}-\mathrm{R}_{626}-$heterocyclyl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{526}\mathrm{R}_{726}$;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{926}-\mathrm{Z}-\mathrm{R}_{626}-$alkyl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{926}-\mathrm{Z}-\mathrm{R}_{626}-$alkenyl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{926}-\mathrm{Z}-\mathrm{R}_{626}-$aryl;
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{926}-\mathrm{Z}-\mathrm{R}_{626}-$heteroaryl; and
- $-\mathrm{R}_{426}-\mathrm{NR}_{826}-\mathrm{CR}_{326}-\mathrm{NR}_{926}-\mathrm{Z}-\mathrm{R}_{626}-$heterocyclyl;

R$_{226}$ is chosen from:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -alkyl-Y-alkyl;
- -alkyl-Y- alkenyl;
- -alkyl-Y-aryl; and
- - alkyl or alkenyl substituted by one or more substituents chosen from:
    - -OH;

-halogen;
-N(R_{526})$_2$;
-CO-N(R_{526})$_2$;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

each R_{326} is =O or =S;

each R_{426} is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each R_{526} is independently H or C_{1-10} alkyl;

R_{626} is a bond, alkyl, or alkenyl, which may be interrupted by one or more –O– groups;

R_{726} is H, C_{1-10} alkyl which may be interrupted by a hetero atom, or R_{726} can join with R_{526} to form a 5 to 7 membered heterocyclic ring;

R_{826} is H, C_{1-10} alkyl, arylalkyl, or R_{426} and R_{826} can join together to form a 5 to 7 membered heterocyclic ring;

R_{926} is C_{1-10} alkyl which can join together with R_{826} to form a 5 to 7 membered heterocyclic ring;

each **Y** is independently –O– or –S(O)$_{0-2}$–;

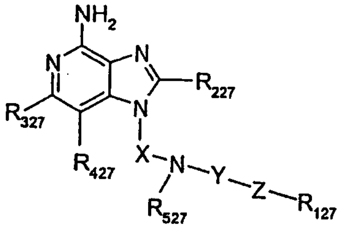
Z is a bond, –CO–, or –SO$_2$–;

v is 0 to 4; and

each R_{26} present is independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen, and trifluoromethyl;

and pharmaceutically acceptable salts of any of the foregoing.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines compounds defined by Formula XXVII



XXVII

wherein X is alkylene or alkenylene;

Y is –CO–, –CS–, or –SO_2–;

Z is a bond, –O–, –S–, or –NR_{527}–;

R_{127} is aryl, heteroaryl, heterocyclyl, C_{1-20} alkyl or C_{2-20} alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently chosen from:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$ -alkyl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-heterocyclyl;

-$(alkyl)_{0-1}$-$N(R_{527})_2$;

-$(alkyl)_{0-1}$-NR_{527}-CO-O-alkyl;

- -(alkyl)$_{0-1}$-NR$_{527}$-CO-alkyl;
- -(alkyl)$_{0-1}$-NR$_{527}$-CO-aryl;
- -(alkyl)$_{0-1}$-NR$_{527}$-CO-heteroaryl;
- -N$_3$;
- -halogen;
- -haloalkyl;
- -haloalkoxy;
- -CO-haloalkyl;
- -CO-haloalkoxy;
- -NO$_2$;
- -CN;
- -OH;
- -SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R$_{227}$ is chosen from:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -alkyl-O-alkyl;
- -alkyl-S-alkyl;
- -alkyl-O-aryl;
- -alkyl-S-aryl:
- -alkyl-O- alkenyl;
- -alkyl-S- alkenyl; and
- -alkyl or alkenyl substituted by one or more substituents chosen from:
    - -OH;
    - -halogen;
    - -N(R$_{527}$)$_2$;
    - -CO-N(R$_{527}$)$_2$;
    - -CS-N(R$_{527}$)$_2$;
    - -SO$_2$-N(R$_{527}$)$_2$;
    - -NR$_{527}$-CO-C$_{1-10}$ alkyl;

-NR_{527}-CS-C_{1-10} alkyl;
-NR_{527}-SO_2-C_{1-10} alkyl;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

R_{327} and **R_{427}** are independently chosen from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;

each **R_{527}** is independently H or C_{1-10}alkyl;

and pharmaceutically acceptable salts thereof.

As used herein, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl and adamantyl.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, and the like.

In some embodiments, the topical formulations of the present invention are prepared using the free base form of the IRM compound.

The amount of an IRM compound that will be therapeutically effective in a specific situation will depend on such things as the activity of the particular compound, the dosing regimen, the application site, the particular formulation and the condition being treated. As such, it is generally not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to these compounds, and routine testing. The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, inhibition of TH2 immune response, antiviral or antitumor activity, reduction or elimination of postsurgical scarring, or reduction or resolution of actinic keratosis or pre-actinic keratosis lesions.

In general, the amount of the IRM compound present in a topical formulation of the invention will be an amount effective to treat a targeted condition, to prevent recurrence of the condition, or to promote immunity against the condition. The amount or concentration of the IRM compound can range from 0.001% to 10% by weight based on the total formulation weight, such as, for example, from 0.03% to 5.0% by weight, or from 0.1 to 1.0% by weight. In certain embodiments, the amount of the IRM compound is at least 0.003% by weight, such as, for example, at least 0.005%, at least 0.01%, at least 0.03%, at least 0.10%, at least 0.30% and at least 1.0%. In other embodiments, the amount of the IRM compound is at most 5.0% by weight, such as, for example, at most 3.0%, and at most 1.0%.

The topical formulations of the invention additionally comprise a fatty acid. As used herein, the term "fatty acid" means a carboxylic acid, either saturated or unsaturated, comprising 6 to 28 carbon atoms, such as, for example, from 10 to 22 carbon atoms. Non-limiting examples of such fatty acids include isostearic acid, oleic acid, and linear- or- branched chained carboxylic acids of 6 to 18 carbon atoms. The fatty acid may be present in the formulation in an amount sufficient to solubilize the IRM compound. In one embodiment, the amount of the fatty acid can range from 0.05 % to 40 % by weight based on the total weight of the formulation, such as, for example, from 1% to 30%, from 3% to 15% and from 5% to 10%. In certain embodiments, the amount of the fatty acid is at least 3.0% by weight, such as, for example, at least 5.0%, at least 10.0%, and at least 25%. The fatty acid component of the formulation can comprise one or more fatty acids.

The topical formulations of the invention additionally comprise at least one hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms. By "hydrophobic" is meant that the component is essentially insoluble in water, i.e. immiscible with water and unable to form a micelle in water, and does not contain polyoxyethylene or acid salt groups. Preferably the hydrophobic, aprotic component has a hydrophilic lipophilic balance (HLB) of less than 2. The HLB of a component may be determined as described, for example, in Attwood, D., Florence, A. T. Surfactant Systems: Their Chemistry, Pharmacy, and Biology. New York: Chapman & Hall, 471-473, 1983. By "aprotic" is meant that the component cannot donate a proton to the IRM and does not contain groups such as carboxyl, hydroxy, primary and secondary amino, primary and secondary amido, or quaternary ammonium groups. Preferably this component has a pKa of at least 14.2 and does not substantially solubilize or form a complex such as an acid-base pair or complex or a hydrogen bond complex with the IRM compound. By "not substantially" is meant that the ratio of the IRM compound's solubility in the hydrophilic, aprotic component to that in isostearic acid is less than 1:40.

Formulations intended for dermal or topical use desirably have a certain minimum amount of an oil phase to provide qualities such as spreadability, feel on the skin, texture, and so on. However, if all the components of the oil phase solubilize the IRM, then the degree of saturation of the IRM in the formulation will decrease, making it more difficult to deliver the IRM from the formulation to the skin. Addition of the hydrophobic, aprotic component can increase the oil phase volume of the topical formulation to provide desirable qualitites such as spreadability and feel, while at the same time not appreciably altering the degree of saturation or thermodynamic activity of the IRM. For example, the amount of fatty acid, which solubilizes the IRM, can be reduced to increase the degree of IRM saturation while maintaining a sufficient oil phase volume by virtue of the addition of the hydrophobic, aprotic component, which does not offset the increased IRM saturation. Thus, the topical formulation of the present invention can facilitate both physical property and drug delivery requirements. Degree of saturation and thermodynamic activity of the IRM in these formulations is equal to the IRM concentration in the oil phase divided by the saturation concentration of the IRM in the oil phase. When the topical formulations of the present invention contain saturated IRM the thermodynamic activity or degree of saturation is unity, and when partially saturated the thermodynamic activity or degree of saturation is less than unity.

The amount of the hydrophobic, aprotic component present in a formulation of the invention can range from 1% to 30% by weight based on the total formulation weight, for example, from 3 % to 15% by weight, and from 5 to 10% by weight. In certain embodiments, the amount of the hydrophobic, aprotic component is at least 3.0% by weight, for example, at least 5.0%, and at least 10.0%. The weight ratio of the hydrophobic, aprotic component to the fatty acid can be 0.025:1 to 600:1, for example, 0.5:1 to 50:1, and 2:1 to 30:1. The combined amount (weight percent of the total topical formulation weight) of the hydrophobic, aprotic component and the fatty acid can be 2% to 50% by weight, for example 2% to 30%, 5% to 30%, 5% to 20%, and 10% to 20%.

Examples of useful hydrophobic, aprotic components include but are not limited to fatty acid esters, for example, isopropyl mysristate, isopropyl palmitate, diisopropyl dimer dilinoleate; triglycerides, for example, caprylic/capric triglyceride; cetyl esters wax; hydrocarbons of 8 or more carbon atoms, for example, light mineral oil, white petrolatum; and waxes, for example, beeswax. In some embodiments, the hydrophobic, aprotic component is chosen from one or more of isopropyl mysristate, isopropyl palmitate, caprylic/capric triglyceride, and diisopropyl dimer dilinoleate.

The formulations of the present invention can also comprise a hydrophilic viscosity enhancing agent. Examples of suitable hydrophilic viscosity enhancing agents include cellulose ethers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose; polysaccharide gums such as xanthan gum; and homopolymers and copolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythriol such as those polymers designated as carbomers in the

United States Pharmacopoeia. Suitable carbomers include, for example, those available as Carbopol™ 934P, Carbopol 971P, Carbopol 940, Carbopol 974P, Carbopol 980, and Pemulen™ TR-1 (USP/NF Monograph; Carbomer 1342), all available from Noveon, Cleveland, Ohio. In one embodiment of the present invention, the viscosity enhancing agent is chosen from Carbopol 974P and 980. When included, the viscosity enhancing agent is generally present in an amount ranging from 0.1% to 10% by weight of total formulation weight, such as, for example, from 0.5 % to 5% by weight, from 0.5% to 1.5% by weight, and from 0.7% to 3% by weight. In certain embodiments, the amount of the viscosity enhancing agent is at least 0.5% by weight, for example, at least 0.6% by weight, at least 0.7% by weight, at least 0.9% by weight, and at least 1.0% by weight.

The formulations of the invention can additionally comprise an emulsifier. Suitable emulsifiers include non-ionic surfactants such as, for example, polysorbate 60, sorbitan monostearate, polyglyceryl-4 oleate, polyoxyethylene(4) lauryl ether, etc. In certain embodiments, the emulsifier is chosen from poloxamers (e.g., Pluronic™ F68, also known as Poloxamer 188, a poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol), available from BASF, Ludwigshafen, Germany) and sorbitan trioleate (e.g., Span 85 available from Uniqema, New Castle, DE). If included, the emulsifier is generally present in an amount of 0.1% to 10% by weight of total formulation weight, for example, from 0.5% to 5% by weight, and from 0.75% to 3.5% by weight. In certain embodiments, the amount of the emulsifier is at least 1.0% by weight, for example, at least 2.5%, at least 3.5%, and at least 5.0%.

In certain embodiments of the present invention, the formulation can also include at least one chelating agent. The chelating agent functions to chelate metal ions that may be present in the formulation. Suitable chelating agents include salts of ethylenediaminetetraacetate (EDTA), such as the disodium salt. If included, the chelating agent is generally present in an amount ranging from 0.001 % to 0.1% by weight, and preferably from 0.01% to 0.05% by weight. In certain embodiments, the amount of the chelating agent is at least 0.005% by weight, such as, for example, at least 0.01%, and at least 0.05%.

The formulation can also include a preservative system. The preservative system is generally comprised of at least one preservative compound chosen from methylparaben, ethylparaben, propylparaben, phenoxyethanol, iodopropynyl butylcarbamate, sorbic acid, a fatty acid monoester of glycerin such as glycerol monolaurate, and a fatty acid monoester of propylene glycol such as propylene glycol monocaprylate. The preservative system may also include a preservative enhancing solubilizer which enhances the solubility of the preservative in the aqueous phase, examples of which include diethylene glycol monoethyl ether and propylene glycol. In one embodiment, the preservative system can be comprised of methylparaben, propylparaben, and propylene glycol. In another embodiment, the preservative system can be comprised of methylparaben, ethylparaben, and diethylene glycol monoethyl ether. In one embodiment, the preservative system can be comprised of phenoxyethanol, methylparaben or methyl- and ethylparaben, and diethylene glycol monoethyl ether. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate, diethylene glycol monoethyl ether, and poly(ethylene glycol)(4) monolaurate. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate, one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol, and diethylene glycol monoethyl ether. In the above embodiments, the methylparaben, ethylparaben, and propylparaben can each be present in the formulations in an amount ranging from 0.01% to 0.5% by weight of the formulation weight, for example, from 0.05 % to 0.25% by weight, and from 0.1% to 0.2% by weight. The iodopropynyl butylcarbamate can be present in the formulations in an amount ranging from 0.01% to 0.1%. The phenoxyethanol can be present in the formulations in an amount ranging from 0.1% to 1%. The propylene glycol and diethylene glycol monoethyl ether can each be present in the formulations in an amount ranging from 1% to 30% by weight of the formulation weight, such as, for example, from 5 % to 25% by weight, and from 10% to 15% by weight. The preservative system can be present in the formulations in an amount ranging from 0.01% to 30% by weight of the formulation weight, for example, from 0.05% to 30%, from 0.1% to 25% by weight, and from 0.2% to 15% by weight. In a further embodiment, the methylparaben, ethylparaben, propylparaben, iodopropynyl butylcarbamate, and phenoxyethanol can be solubilized in propylene glycol, poly(ethylene glycol)(4) monolaurate, or diethylene glycol monoethyl ether prior to addition to the formulation. The preservative system can be selected such that it meets the criteria for antimicrobial effectiveness set forth in the United States Pharmacopeia <51>.

The formulations of the present invention may additionally comprise at least one pH adjuster. Suitable pH adjusters include organic bases and inorganic bases such as, for example, KOH, NaOH. The pH of the topical formulations of the present invention generally ranges from 3.5 to 7.0. In one embodiment, the pH of the topical formulations of the present invention can range from 4.0 to 6.0, preferably 5.0. In another embodiment of the invention, the pH of the topical formulations of the present invention can range from 5.5 to 6.5, preferably 6.0.

Any of the foregoing formulations can be in the form of an oil-in-water emulsion such as a cream or a lotion. Such an emulsion can comprise an oil phase comprising the IRM compounds, a fatty acid in an amount sufficient to solubilize the IRM compounds, a hydrophobic, aprotic component; and an aqueous phase comprising a hydrophilic viscosity enhancing agent, for example, a carbomer. In certain embodiments, the amount or concentration of the IRM in the oil phase can be at least 0.01%, for example, at least 0.02%, at least 0.1%, and at least 1% with respect to oil phase weight. In other embodiments, the amount or concentration of the IRM in the oil phase can be at most 20%, for example, at most 10%, and at most 5% with respect to oil phase weight. The emulsion can be preserved so that when challenged by an antimicrobial effectiveness test, it meets regulatory requirements for topical creams packaged in multiple-use containers.

Any of the foregoing formulations according to the present invention can be applied to the dermal surfaces of a mammal. Depending on the IRM compound concentration, formulation composition, and dermal surface, the therapeutic effect of the IRM compound may extend only to the superficial layers of the dermal surface or to tissues below the dermal surface. Thus, another aspect of the present invention is directed to a method for the treatment of a dermal associated condition comprising applying to skin one of the foregoing formulations. As used herein, a "dermal associated condition" means an inflammatory, infectious, neoplastic or other condition that involves a dermal surface or that is in sufficient proximity to a dermal surface to be affected by a therapeutic agent topically applied to the dermal surface. Examples of a dermal associated condition include warts, atopic dermatitis, basal cell carcinoma, postsurgical scars, and actinic keratosis.

In one embodiment, the formulations can be applied to the surface of skin for treatment of actinic keratosis (AK). Actinic keratoses are premalignant lesions considered biologically to be either carcinoma in-situ or squamous intraepidermal neoplasia. AK is the most frequent epidermal tumor and is induced by ultraviolet (UV) radiation, typically from sunlight. Because of its precancerous nature, AK may be considered the most important manifestation of sun-induced skin damage.

In some embodiments, the above described formulations are particularly advantageous for dermal application for a period of time sufficient to obtain a desired therapeutic effect without undesired systemic absorption of the IRM.

EXAMPLES

The following Examples are provided to further describe various IRM formulations and methods according to the invention. The examples, however, are not intended to limit the formulations and methods within the spirit and scope of the invention.

Examples 1-7 and Comparative Example C1

Table 1 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis.

TABLE 1

Ingredient (Compendial Status)	Topical Cream (percentage weight-by-weight)							
	Comparative Example C1 (Placebo)	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
IRM Compound 1	0.00	0.001	0.003	0.010	0.03	0.10	0.30	1.00
Isostearic Acid	5.00	5.00	5.00	5.00	5.00	5.00	7.00	10.00
Isopropyl Myristate (NF)	10.00	10.00	10.00	10.00	10.00	10.00	8.00	5.00
Carbomer 974P (NF)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Poloxamer 188 (NF)	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Propylene Glycol (USP)	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Methylparaben (NF)	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Propylparaben (NF)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Edetate Disodium (USP)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Hydroxide (NF) Solution, 20% w/w	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.55
Purified Water (USP)	65.65	65.649	65.647	65.64	65.62	65.55	65.35	64.60
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

The formulations set forth in Table 1 were prepared in the following manner:

Oil phase preparation: 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (IRM compound 1) was dissolved in isostearic acid and isopropyl myristate, with heat if necessary. Carbomer 974P was then dispersed in the oil phase.

Water phase preparation: Edetate disodium was dissolved in the water. Methylparaben and propylparaben were dissolved in propylene glycol and the solution was subsequently added to the water phase. Poloxamer 188 was then added to the water phase and mixed until dissolved.

Phase combination: The oil phase was added to the water phase at ambient conditions. The emulsion was then homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

Formulations containing 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (IRM Compound 1) were tested for their ability to induce increases in cytokine concentrations in rats following topical application. This study was undertaken to evaluate cytokine induction following a single dosing of various strengths and timepoints or a multiple vs. single dosing of IRM Compound 1. The formulations described above were tested by examining tissue and serum concentrations of TNF-α, MCP-1 (monocyte chemoattractant protein-1) and IFN-α cytokines following drug treatment.

Female CD hairless rats (Charles River Laboratories, Wilmington, MA) weighing 200-250 grams were used in all studies. Animals were randomized to treatment groups and dosed five per treatment group.

The rats were acclimated to collars around the neck on two consecutive days prior to actual dosing. The rats were collared before dosing to prevent ingestion of the drug, and were then dosed topically with 50 μL of active cream or the appropriate placebo on right flank and then housed individually following dosing. At various times following dosing, the rats were anesthetized and blood was collected by cardiac puncture. Blood was allowed to clot at room temperature and serum was separated from the clot via centrifugation and stored at –20 °C until it was analyzed for cytokine concentrations.

Following blood collection, the rats were euthanized and their skins removed. Tissue from both treated site (at) and contralateral site (away) were obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial and flash frozen in liquid nitrogen. The frozen tissue sample was then suspended in 1.0 mL RPMI medium (Celox, Hopkins, MN) containing 10% fetal bovine serum (Sigma, St. Louis, MO), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue was homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, OK) for approximately 1 minute. The tissue suspension was then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris, and the supernatant collected and stored at –20 °C until analyzed for cytokine concentrations.

ELISAs for rat MCP-1 were purchased from BioSource Intl. (Camarillo, CA) and rat TNF-α were purchased from BD Pharmingen (San Diego, CA) and performed according to manufacturer's specifications. Results for both TNF-α, and MCP-1 were expressed in pg/200 mg tissue or pg/ml serum. The sensitivity of the TNF-α ELISA was 31.2 pg/ml and of the MCP-1 ELISA was 11.7 pg/ml. IFN-α concentrations in both serum and skin tissue were determined using a bioassay that measured inhibition of the viral cytopathic effect of vesicular stomatitis virus on rat LMS-C2 fibroblast cells as previously described (Reiter, M. J., Testerman, T. L., Miller, R. L., Weeks, C. E., and Tomai, M. A. (1994) "Cytokine Induction in Mice by the Immunomodulator Imiquimod." J. Leukocyte Biol. 55, 234-240). IIT Research Institute, Chicago IL, performed these assays. Results for IFN-α concentrations were normalized to a standard reference rat IFN-α, preparation with results being reported in U/mL and are normalized per mg of tissue.

The data shown below in Tables 2-4 are from three separate experiments and analyzed to 1) measure pharmacokinetics by full time course, 2) measure dose response and 3) measure multiple vs. single dosing.

In order to determine the kinetics of local and systemic cytokine production following local administration of IRM Compound 1, the full time course study (Study 1 with results in Table 2) was done by topically dosing rats with the topical cream formulation of Example 7.

Serum and tissue samples were taken at 1, 2, 4, 8, 16, 24 and 48 hours post dose. Multiple cytokines (MCP-1, TNF-α and IFN-α) were analyzed separately.

With the tissue data, for each hour measured, a paired t-test (used to eliminate within subject variability) analyzed the difference between treated tissue and control tissue from the same animal. A p-value less than alpha=0.05 indicated a statistically significant difference between the treated and control tissue at that hour. The data are presented in Table 2.

Table 2. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 7 Full Time Course[a]

Time (hours) Post Dose	Dose	Cytokine Concentration[b]		
		TNF-α		
		Serum	Treated Site	Control site
0	untreated	0	NA	96±5
16	placebo	0	103±8	71±6
1	1%	6±6	318±33[c]	96±13
2	1%	0	1125±74[c]	124±18
4	1%	0	1120±51[c]	129±11
8	1%	24±16	429±56[c]	91±12
16	1%	6±4	231±22[c]	87±27
24	1%	32±32	198±28[c]	103±13
48	1%	49±49	74±10	69±15
		MCP-1		
0	untreated	81±30	NA	44±2
16	placebo	144±9	144±41	42±3
1	1%	86±29	40±8	42±3
2	1%	123±31	234±29[c]	50±4
4	1%	101±28	723±89[c]	41±5
8	1%	438±91[c]	1474±202[c]	38±3
16	1%	424±96[c]	1209±325[c]	31±5
24	1%	187±39	813±151[c]	39±1
48	1%	141±24	145±48[c]	36±6
		IFN-α		
0	untreated	<200	NA	<650
16	placebo	<200	<650	<650
1	1%	<200	<650	<650
2	1%	<200	<650	<650
4	1%	<200	<650	<650
8	1%	<200	3/5≥650	<650
16	1%	<200	<650	<650
24	1%	<200	<650	<650
48	1%	<200	<650	<650

[a] Female hairless CD rats were dosed topically with cream formulated Compound 1.

[b] TNF-α and MCP-1 were measured by ELISA. IFN-α was measured by bioassay. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.

[c] Indicates $p<0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

A multiple dose study was done to monitor effects of a multiple dose regimen (Study 2 with results shown in Table 3). Rats were dosed two times a week for six hours for three weeks with topical cream formulation of Example 5. Placebo (Comparative Example C1) and single dosed rats were done for comparison and done simultaneously with the last dosing of the multiple dose set. Serum and tissue samples were taken at 8 and 24 hours post dose and analyzed for MCP-1.

An analysis identical to that of Study 1 was performed for Study 2. This data set was broken up by treatment (multiple- or single-use) and time point prior to analysis. Again, placebo data were recorded only at the 8-hour time point for single use, but were used to compare placebo to every treatment and time point combination separately. The results are set forth in Table 3 below.

Table 3. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 5 Multiple vs. Single Dose[a]

Time (hours) Post Dose	Dose	Cytokine Concentration[b]		
		MCP-1		
		Serum	Treated Site	Control Site
0	None (untreated)	89±11	NA	20±10
24	Placebo	41±14	42±15	28±6
8	Multiple 0.1%	71±13	784±48[c]	42±5[c]
24	Multiple 0.1%	105±36	145±23[c]	32±6
8	Single 0.1%	73±9	519±99[c]	33±6
24	Single 0.1%	82±3[c]	412±130[c]	35±7

[a] Female hairless CD rats were dosed topically with cream formulated Compound 1.
[b] MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c] Indicates $p<0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

A dose response study (Study 3 with results shown in Table 4) was performed by dosing with the topical cream formulations of Examples 3-5 and 7, containing various concentrations of IRM Compound 1. Serum and tissue samples were taken at 8 and 24 hours post dose and analyzed for MCP-1. The studies tested topical delivery of creams comprising IRM Compound 1 for its ability to affect a local MCP-1 induction at four concentrations.

Serum data compared active treatment to placebo (Comparative Example C1) separately at each specified time point. Note that the placebo group was only measured at 24 hours post dose and these observations were compared to each time point for the active group.

Table 4. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Formulations of Examples 3-5 and 7 [a]

Time (hours) Post Dose	Dose	Cytokine Concentration[b] MCP-1		
		Serum	Treated Site	Control Site
0	controls	207±96	NA	38±12
24	placebo (Comparative Example C1)	367±178	61±14	20±5
8	0.01% (Example 3)	81±23	61±12	36±7
8	0.03% (Example 4)	81±20	271±29	48±5
8	0.1% (Example 5)	153±14	1119±122[c]	51±8
8	1.0% (Example 7)	136±23	1370±99[c]	50±15
24	0.01% (Example 3)	71±18	183±49[c]	33±13
24	0.03% (Example 4)	71±20	212±49[c]	40±7
24	0.1% (Example 5)	226±73	628±127[c]	40±11
24	1.0% (Example 7)	149±45	756±38[c]	30±9

[a] Female hairless CD rats were dosed topically with cream formulated Compound 1.

[b] MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.

[c] Indicates $p<0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

Examples 8-13

Table 5 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis.

TABLE 5

Ingredient (Compendial Status)	Topical Cream (percentage weight-by-weight)					
	Example 8	Example 9	Example 10	Example 11	Example 12	Example 13
IRM Compound 2	0.01	0.03	0.10	1.00	0.003	0.30
Isostearic Acid	5.00	5.00	5.00	10.00	5.00	5.00
Isopropyl Myristate (NF)	10.00	10.00	10.00	5.00	10.00	10.00
Carbomer 974P (NF)	1.00	1.00	1.00	0.75	1.00	1.00
Poloxamer 188 (NF)	2.50	2.50	2.50	2.50	2.50	2.50
Propylene Glycol (USP)	15.00	15.00	15.00	15.00	15.00	15.00
Methylparaben (NF)	0.20	0.20	0.20	0.20	0.20	0.20
Propylparaben (NF)	0.10	0.10	0.10	0.10	0.10	0.10
Edetate Disodium (USP)	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Hydroxide (NF) Solution, 20% w/w	0.50	0.50	0.50	0.35	0.50	0.50
Purified Water (USP)	65.64	65.62	65.55	65.05	65.647	65.35
Total	100.00	100.00	100.00	100.00	100.00	100.00

The formulations set forth in Table 5 were prepared in the following manner:

Oil phase preparation: N-[4-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*] [1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea (IRM Compound 2) was dissolved in isostearic acid and isopropyl myristate, with heat if necessary. Carbomer 974P was then dispersed in the oil phase.

Water phase preparation: Edetate disodium was dissolved in the water. Methylparaben and propylparaben were dissolved in propylene glycol, and the solution was subsequently added to the water phase. Poloxamer 188 was then added to the water phase and mixed until dissolved.

Phase combination: The oil phase was added to the water phase at ambient conditions. The emulsion was then homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured, and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

Formulations containing N-[4-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea (IRM Compound 2) were tested for their ability to induce increases in cytokine concentrations in rats following topical application. This study was undertaken to evaluate cytokine induction following a single dosing of various strengths and timepoints or a multiple vs. single dosing of IRM Compound 2. The formulations described above were tested by examining tissue and serum concentrations of TNF-α, MCP-1 and IFN-α following drug treatment as described in Examples 1-7.

The data shown below in Tables 6-8 are from three separate experiments and analyzed to 1) measure pharmacokinetics by full time course, 2) measure dose response and 3) measure multiple vs. single dosing.

In order to determine the kinetics of local and systemic cytokine production following local administration of IRM Compound 2, the full time course study (Study 1 with results in Table 6) was done by topically dosing rats with the topical cream formulation of Example 11 as described in Examples 1-7. The data are presented in Table 6.

Table 6. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 11 Full Time Course[a]

Time (hours) Post Dose	Dose	Cytokine Concentration[b]		
		TNF-α		
		Serum	Treated Site	Control site
0	untreated	29±15	NA	70±11
16	placebo	42±9	131±32	69±11
1	1%	38±38	44±14	35±19
2	1%	2±2	75±20[c]	33±13
4	1%	3±3	321±18[c]	62±20
8	1%	0	894±180[c]	21±9
16	1%	12±12	377±45[c]	22±12
24	1%	16±8	285±15[c]	52±14
48	1%	24±7	74±9	65±13
		MCP-1		
0	untreated	100±20	NA	33±7
16	placebo	144±9	225±106	22±4
1	1%	117±17	56±9	55±9
2	1%	126±29	50±13	54±8
4	1%	136±29	161±18[c]	71±9
8	1%	189±28	1020±319	45±15
16	1%	297±35	1294±122[c]	40±9
24	1%	217±12	1044±185[c]	41±11
48	1%	120±22	134±14[c]	34±7
		IFN-α		
0	untreated	<65	NA	<650
16	placebo	<65	<650	<650
1	1%	<65	<650	<650
2	1%	<65	<650	<650
4	1%	<65	<650	<650
8	1%	<65	901±571	<650
16	1%	<65	1330±386[c]	<650
24	1%	<65	<650	<650
48	1%	<65	<650	<650

[a] Female hairless CD rats were dosed topically with cream formulated Compound 2.

[b] TNF-α and MCP-1 were measured by ELISA. IFN-α was measured by bioassay. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.

[c] Indicates $p<0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

A multiple dose study was done to monitor effects of a multiple dose regimen (Study 2 with results shown in Table 7). Rats were dosed two times a week for six hours for three weeks with topical cream formulation of Example 10. Placebo (Comparative Example C1) and single dosed rats were done for comparison and done simultaneously with the last dosing of the multiple dose set. Serum and tissue samples were taken at 16 and 24 hours post dose and analyzed for MCP-1.

An analysis identical to that of Study 1 was performed for Study 2. This data set was broken up by treatment (multi or single use) and time point prior to analysis. Again, placebo data were recorded only at the 16-hour time point for single use, but were used to compare placebo to every treatment and time point combination separately. The results are set forth in Table 7 below.

Table 7. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 10 Multiple vs. Single Dose[a]

Time (hours) Post Dose	Dose	Cytokine Concentration[b] MCP-1		
		Serum	Treated Site	Control Site
0	None (untreated	161±58	NA	80±22
16	Placebo	214±35	71±16	47±11
16	Multiple 0.1%	321±62	1173±117[c]	86±14
24	Multiple 0.1%	217±43	388±80[c]	58±5
16	Single 0.1%	205±32	1448±241[c]	77±15
24	Single 0.1%	279±45	1172±288[c]	90±15

[a] Female hairless CD rats were dosed topically with cream formulated Compound 2.
[b] MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c] Indicates $p<0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

A dose response study (Study 3 with results shown in Table 8) was performed by dosing with the topical cream formulations of Examples 8-11, containing various concentrations of IRM Compound 2. Serum and tissue samples were taken at 16 and 24 hours post dose and analyzed for MCP-1. The studies tested topical delivery of creams comprising IRM Compound 2 for its ability to affect a local MCP-1 induction at four concentrations.

Serum data compared active treatment to placebo (Comparative Example C1) separately at each specified time point. Note that the placebo group was only measured at 16 hours post dose and these observations were compared to each time point for the active group.

Table 8. Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Formulations of Examples 8-11[a]

Time (hours) Post Dose	Dose	Cytokine Concentration[b] MCP-1		
		Serum	Treated Site	Control Site
0	controls	293±23	NA	41±11
16	placebo (Comparative Example C1)	293±76	44±10	36±12
16	0.01% (Example 8)	276±50	257±85	57±20
16	0.03% (Example 9)	318±86	210±10	45±9
16	0.10% (Example 10)	529±141	2622±616[c]	73±9
16	1.0% (Example 11)	345±51	3166±470[c]	71±11
24	0.01% (Example 8)	298±65	276±87	94±32
24	0.03% (Example 9)	253±34	427±238	28±14
24	0.10% (Example 10)	331±93	1461±264[c]	19±7
24	1.0% (Example 11)	358±52	1952±185[c]	17±6

[a] Female hairless CD rats were dosed topically with cream formulated Compound 2.

[b] MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.

[c] Indicates $p<0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

Examples 14 – 18

Table 9 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

Table 9

Ingredients	Topical Creams (percentage weight-by-weight)				
	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18
IRM Compound 1	0.01	0.10	1.00	3.00	1.00
Isostearic Acid (874)	5.00	5.00	10.00	25.00	10.00
*Diisopropyl dimer dilinoleate	10.00	10.00	5.00	5.00	-
**Caprylic/capric triglycerides	-	-	-	-	5.00
Carbomer 980, NF	0.70	0.70	0.70	0.90	0.70
Diethylene glycol monoethyl ether USA - NF	10.00	10.00	10.00	10.00	10.00
Disodium EDTA, USP	0.05	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.50	2.50	2.50	2.50	2.50
Purified Water	70.94	70.85	69.95	52.55	69.95
Methylparaben, NF	0.20	0.20	0.20	0.20	0.20
Ethylparaben	0.20	0.20	0.20	0.20	0.20
20% (w/w) NaOH	0.40	0.40	0.40	0.60	0.40
Total % w/w	100.00	100.00	100.00	100.00	100.00

*Available under the trade name PRIPURE 3786 from Uniquema, New Castle, DE

**Available under the trade name Crodamol GTCC-PN from Croda, Inc, Parsippany, NJ

Examples 19 – 24

Table 10 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

Table 10

Ingredients	Topical Creams (percentage weight-by-weight)					
	Ex. 19	Ex. 20	Ex. 21	Ex. 22	Ex. 23	Ex. 24
IRM Compound 2	0.003	0.03	0.10	1.00	3.00	1.00
Isostearic Acid (874)	5.00	5.00	5.00	10.00	25.00	10.00
Diisopropyl dimer dilinoleate	10.00	10.00	10.00	5.00	5.00	-
Caprylic/capric triglycerides	-	-	-	-	-	5.00
Carbomer 980, NF	0.70	0.70	0.70	0.70	0.60	0.70
Diethylene glycol monoethyl ether USA - NF	10.00	10.00	10.00	10.00	10.00	10.00
Disodium EDTA, USP	0.05	0.05	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.50	2.50	2.50	2.50	2.50	2.50
Purified Water	70.95	70.92	70.85	69.95	53.19	69.95
Methylparaben, NF	0.20	0.20	0.20	0.20	0.20	0.20
Ethylparaben	0.20	0.20	0.20	0.20	0.20	0.20
20% (w/w) NaOH	0.40	0.40	0.40	0.40	0.26	0.40
Total % w/w	100.00	100.00	100.00	100.00	100.00	100.00

The formulations described in Tables 9 and 10 were prepared using the following general method:

Oil phase preparation:

The IRM compound was dissolved in isostearic acid and diisopropyl dimer dilinoleate (or caprylic/capric acid triglyceride) with heat if necessary.

Water phase preparation:

Edetate disodium was dissolved in the water. Poloxamer 188 was then added to the water phase and mixed until dissolved. Carbomer 980 was then added to the water phase and mixed until the carbomer was fully dispersed and hydrated. Methylparaben and propylparaben were dissolved in diethylene glycol monoethyl ether and the solution was subsequently added to the water phase.

Phase combination:

The water phase was added to the oil phase at ambient conditions. The emulsion was then mixed at high speed or homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

Examples 25 – 28

Table 11 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

Table 11

Ingredient	Topical Cream (percentage weight-by-weight)			
	Ex. 25	Ex. 26	Ex. 27	Ex. 28
IRM Compound 1	1	1	1	1
Isostearic Acid (874)	10	10	10	8
Diisopropyl dimer dilinoleate	5	5	5	1
Carbomer 980, NF	0.7	0.7	0.7	0.7
Diethylene glycol monoethyl ether USA - NF	10	10	10	10
Disodium EDTA, USP	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.5	2.5	2.5	2.5
Purified Water	Qs to 100	Qs to 100	Qs to 100	Qs to 100
Methylparaben, NF	0.2	0.2	0.2	0.2
Ethylparaben	0.2	0.2	0.2	0.2
20% (w/w) NaOH	0.4	0.4	0.4	0.4
10% iodopropynyl butylcarbamate in PEG-4 laurate	-	1	-	-
Phenoxyethanol	-	-	0.5	-

Examples 29 – 135

Topical creams containing the IRM compounds listed in Table 12 were prepared using the general methods described above for Examples 1 – 24. Each IRM was formulated into one or more of the model formulations shown in Tables 13 and 14. Table 15 summarizes the topical creams that were prepared.

Table 12

IRM Compound	Chemical Name
3	1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine
4	1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,8]naphthyridin-4-amine
5	2-butyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,8]naphthyridin-4-amine
6	1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine
7	2-methylthiazolo[4,5-*c*]quinolin-4-amine
8	2-ethoxymethyl-1-phenylmethyl-1*H*-imidazo[4,5-c][1,5]naphthyridin-4-amine
9	2-ethylthiazolo[4,5-*c*]quinolin-4-amine
10	4-amino-2-butyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine-1-ethanol
11	N^1-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]benzamide
12	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine
13	1-(2-phenoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine
14	1-[(R)-1-phenylethyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine
15	N^4-[4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-4-morpholinecarboxamide
16	N^3-[4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]nicotinamide
17	1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine
18	1-[2-(pyridin-4-ylmethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine
19	2-methyl-1-[5-(methylsulfonyl)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine
20	N-[3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl] cyclohexanecarboxamide
21	N-[3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]-2-methylpropanamide
22	N-[3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]butanamide

IRM Compound	Chemical Name
23	2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine
24	N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl} ethanesulfonamide
25	N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl} propanamide
26	1-[2-(methylsulfonyl)ethyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine
27	N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-N'-ethylthiourea
28	2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine
29	2-ethyl-1-[4-(ethylsulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine
30	N-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl} cyclopentanecarboxamide
31	N-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl} morpholine-4-carboxamide
32	1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine
33	8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine
34	4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol
35	2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine
36	2-butyl-1-(2-phenoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine
37	N-[3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl] methanesulfonamide

Table 13

Ingredient	Model Formulation (percentage weight-by-weight)						
	A	B	C	D	E	F	G
IRM	0.01	0.1	1	1	1	1	1
Isostearic acid	5	5	5	20	42	13	6
Isopropyl myristate	10	10	10	10	2	10	10
Carbomer 974P	1	1	1	1	1	1.5	1
Purified water	*	*	*	*	*	*	*
Poloxamer 188	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Propylene glycol	15	15	15	15	13	15	15
Xanthan gum	-	-	-	-	0.4	-	-
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	0.05	0.05	0.05	0.05	0.05	0.05	0.05
20% NaOH	0.7	0.7	0.7	0.7	0.7	0.7	0.7

*Qs to 100

Table 14

Ingredient	Model Formulation (percentage weight-by-weight)					
	H	I	J	K	L	M
IRM	0.01	0.1	1	1	3	5
Isostearic acid	5	5	5	10	10	10
Diisopropyl dimer dilinoleate	10	10	10	5	5	5
Carbomer 980	0.7	0.7	0.7	1.0	1.0	1.0
Purified water	*	*	*	*	*	*
Poloxamer 188	2.5	2.5	2.5	2.6	2.6	2.6
Diethylene glycol monoethyl ether	10	10	10	10	10	10
Xanthan gum	-	-	-	0.1	0.1	0.1
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2
Ethylparaben	0.2	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	0.05	0.05	0.05	0.05	0.05	0.05
20% NaOH	0.4	0.4	0.4	0.4	0.4	0.4

*Qs to 100

Table 15

Example	IRM Compound	Model Formulation
29	3	A
30	3	B
31	3	C
32	4	A
33	4	B
34	4	C
35	5	A

Example	IRM Compound	Model Formulation
36	5	B
37	5	D
38	6	A
39	6	B
40	6	C
41	7	A
42	7	B
43	7	C
44	8	A
45	8	B
46	8	C
47	9	A
48	9	B
49	9	C
50	10	A
51	10	B
52	10	C
53	11	A
54	11	B
55	11	E
56	12	A
57	12	B
58	12	C
59	13	A
60	13	B
61	13	F
62	14	A
63	14	B

Example	IRM Compound	Model Formulation
64	14	G
65	15	H
66	15	I
67	15	K
68	16	H
69	16	I
70	16	K
71	17	A
72	17	B
73	17	C
74	18	H
75	18	I
76	18	K
77	19	H
78	19	I
79	19	K
80	20	H
81	20	I
82	20	K
83	20	L
84	20	M
85	21	H
86	21	I
87	21	K
88	22	H
89	22	I
90	22	J
91	23	H

Example	IRM Compound	Model Formulation
92	23	I
93	23	J
94	24	H
95	24	I
96	24	K
97	25	H
98	25	I
99	25	K
100	26	H
101	26	I
102	26	K
103	27	H
104	27	I
105	27	K
106	28	H
107	28	I
108	28	K
109	29	H
110	29	I
111	29	K
112	30	H
113	30	I
114	30	K
115	31	H
116	31	I
117	31	K
118	32	A
119	32	B

Example	IRM Compound	Model Formulation
120	32	C
121	33	A
122	33	B
123	33	C
124	34	A
125	34	B
126	34	C
127	35	A
128	35	B
129	35	C
130	36	A
131	36	B
132	36	C
133	37	H
134	37	I
135	37	K

The topical creams of Examples 29 –135 were tested using the test method described below. The results are shown in Table 16 below where each value is the mean of the values from the 3 rats in the treatment group.

SINGLE DOSE MCP-1 INDUCTION TEST METHOD

Female CD hairless rats (Charles River Laboratories, Wilmington, MA) weighing 200-250 grams are used. Animals are randomized to treatment groups and dosed three per treatment group.

The rats are acclimated to collars around the neck on two consecutive days prior to actual dosing. A 50 µL dose of active cream or the appropriate placebo is applied to the right flank and gently rubbed into the skin of the rat. The rats are then collared and housed individually to prevent ingestion of the drug. At selected post treatment time points, the rats are anesthetized, and blood (3 mls) is collected by cardiac puncture. Blood is allowed to clot at room temperature. Serum is separated from the clot via centrifugation, and stored at –20°C until it is analyzed for MCP-1 concentration.

Following blood collection, the rats are euthanized, and their skins removed. Tissue samples (4 from each site) from both the treated site and contralateral site (untreated) are obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial, and flash frozen in liquid nitrogen. The frozen tissue sample is then suspended in 1.0 mL RPMI medium (Celox, Hopkins, MN) containing 10% fetal bovine serum (Sigma, St. Louis, MO), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue is homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, OK) for approximately 1 minute. The tissue suspension is then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris, and the supernatant is collected and stored at –20°C until analyzed for MCP-1 concentration.

ELISAs for rat MCP-1 are purchased from BioSource Intl. (Camarillo, CA) and performed according to manufacturer's specifications. Results are expressed in pg/ml, the values for the tissue samples are normalized per 200 mg of tissue. The sensitivity of the MCP-1 ELISA is 12 pg/ml.

Table 16

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
29	123	202	46	291	55	34	142	59
30	119	92	31	177	201	43	142	59
31	212	1235	54	267	606	125	142	59
32	26	54	59	79	82	69	54	56
33	54	70	71	56	74	58	54	56
34	72	88	58	59	319	69	54	56
35	170	110	55	162	142	62	80	58
36	94	674	46	86	1216	96	80	58
37	153	1826	38	136	2036	77	80	58
38	178	65	120	211	121	86	142	59

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
39	193	220	61	259	263	59	142	59
40	226	1204	58	284	1086	95	142	59
41	54	82	96	45	88	71	73	96
42	65	129	78	54	126	88	73	96
43	77	824	68	89	1016	93	73	96
44	86	256	*	177	488	*	128	**28
45	172	1444	*	157	1041	*	128	**28
46	177	1720	*	406	1023	*	128	**28
47	58	53	59	81	95	73	37	73
48	71	200	61	63	112	61	37	73
49	92	1254	62	83	1436	75	37	73
50	170	1033	56	*	655	56	88	*

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
51	625	551	787	*	149	787	88	*
52	811	348	314	*	86	314	88	*
53	70	63	46	76	47	45	7	31
54	68	35	27	71	26	24	7	31
55	75	35	21	44	33	32	7	31
56	115	44	*	115	425	*	201	**42
57	119	411	*	267	1252	*	201	**42
58	190	1560	*	476	1508	*	201	**42
59	155	46	36	271	41	53	107	54
60	123	53	58	175	80	69	107	54
61	133	172	52	151	1131	46	107	54
62	143	211	55	174	428	61	96	26

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
63	320	1614	51	230	1217	74	96	26
64	970	1094	529	425	390	99	96	26
65	43	34	57	46	81	61	83	59
66	29	73	28	32	42	74	83	59
67	19	54	61	25	34	72	83	59
68	60	77	82	91	72	35	68	72
69	143	74	52	99	73	59	68	72
70	59	77	34	91	134	60	68	72
71	259	79	62	134	84	57	177	53
72	138	255	65	122	990	63	177	53
73	251	999	63	293	1411	108	177	53
74	99	66	71	73	99	89	61	91

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
75	76	101	78	3	170	73	61	91
76	66	6779	64	188	4949	104	61	91
77	28	47	35	21	43	40	30	38
78	27	35	37	33	49	59	30	38
79	24	41	40	27	50	38	30	38
80	51	59	23	50	163	0	97	15
81	9	0	15	83	34	10	97	15
82***	61	32	0	121	303	45	97	15
82***	50	149	36	79	225	76	93	120
83	110	164	124	61	275	172	93	120
84	59	177	92	98	629	40	93	120
85	81	0	0	0	0	0	177	0

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
86	116	0	0	0	0	0	177	0
87	69	0	0	0	0	0	177	0
88	114	56	41	87	43	42	141	33
89	74	47	49	132	49	40	141	33
90	91	96	47	111	109	41	141	33
91	42	91	53	86	874	57	34	46
92	83	1238	74	92	1087	67	34	46
93	98	2037	64	114	1124	74	34	46
94	102	98	107	48	136	133	110	100
95	49	130	90	95	158	112	110	100
96	68	255	79	132	528	81	110	100
97	34	88	106	54	95	92	36	102

Cream of Example	MCP-1 (pg/ml)							
	IRM Cream						Placebo Cream	
	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
98	17	116	108	83	123	91	36	102
99	51	150	89	43	945	76	36	102
100	111	81	83	55	115	72	82	58
101	33	72	55	75	209	64	82	58
102	79	489	54	112	3199	103	82	58
103	82	88	69	31	107	94	7	61
104	13	66	55	61	72	63	7	61
105	75	83	87	54	60	69	7	61
106	72	96	103	64	168	158	8	137
107	21	129	98	48	168	75	8	137
108	95	314	72	135	3267	128	8	137
109	72	60	71	71	78	62	12	31

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
110	44	76	57	92	72	75	12	31
111	70	143	83	32	2397	68	12	31
112	66	67	120	28	84	70	30	102
113	46	107	106	70	1034	93	30	102
114	14	627	65	196	2880	111	30	102
115	39	38	41	84	77	90	84	157
116	73	81	90	64	57	223	84	157
117	66	113	52	79	91	61	84	157
118	132	59	59	135	46	52	*	*
119	123	184	31	144	104	42	*	*
120	124	1261	45	171	892	56	*	*
121	90	74	51	88	96	75	78	57

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
122	72	415	50	91	613	82	78	57
123	156	1502	52	226	1043	48	78	57
124	92	94	27	96	95	110	97	652
125	123	198	128	107	72	120	97	652
126	136	1828	97	73	1348	349	97	652
127	67	66	46	81	90	22	51	81
128	63	80	58	55	53	35	51	81
129	49	382	58	35	809	59	51	81
130	132	55	41	135	162	43	74	32
131	124	279	59	144	822	60	74	32
132	124	1901	13	171	1212	11	74	32
133	64	106	0	52	199	32	26	8

MCP-1 (pg/ml)								
	IRM Cream						Placebo Cream	
Cream of Example	6 hours			24 hours				
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
134	9	76	0	70	59	0	26	8
135	59	89	0	76	47	0	26	8

*MCP-1 concentration was not measured

**MCP-1 concentration is for the treated site.

***The cream of Example 82 was used in 2 separate experiments

Examples 136 – 140

Table 17 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

Table 17

Ingredients	Topical Creams (percentage weight-by-weight)				
	Ex. 136	Ex. 137	Ex. 138	Ex. 139	Ex. 140
IRM Compound 1	1	1	1	1	1
Isostearic Acid	10	10	8	10	10
Diisopropyl dimer dilinoleate	-	5	1	5	5
Caprylic/capric triglycerides	5	-	-	-	-
Carbomer 980	0.7	0.7	0.7	0.7	0.7
Diethylene glycol monoethyl ether	10	10	10	10	10
Disodium EDTA	0.05	0.05	0.05	0.05	0.05
Poloxamer 188	2.5	2.5	2.5	2.5	2.5
Purified Water	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100
Methylparaben	0.2	0.1	0.2	0.2	0.2
Ethylparaben	0.2	0.1	0.2	0.2	0.2
20% (w/w) NaOH	Qs to pH 5 – 5.5	Qs to pH 5 – 5.5	Qs to pH 5 – 5.5	Qs to pH 6.5	Qs to pH 5 – 5.5
Iodopropynyl butylcarbamate	-	0.1	-	-	-
PEG-4 Laurate	-	0.9	-	-	-
Phenoxyethanol	-	1	-	-	-
Sorbic acid	-	0.15	-	-	-

The topical creams of Examples 136 –140 were tested using the test method described below. The results are shown in Table 18 below where each value is the mean of the values from the 3 rats in the treatment group. "Normal animals" did not receive any treatment.

SINGLE DOSE CYTOKINE INDUCTION TEST METHOD

Female CD hairless rats (Charles River Laboratories, Wilmington, MA) weighing 200-250 grams are used. Animals are randomized to treatment groups and dosed three per treatment group.

The rats are acclimated to collars around the neck on two consecutive days prior to actual dosing. A 50 µL dose of active cream is applied to the right flank and gently rubbed into the skin of the rat. The rats are then collared and housed individually to prevent ingestion of the drug. At 6 hours post treatment, the rats are anesthetized, and blood (3 mls) is collected by cardiac puncture. Blood is allowed to clot at room temperature, serum is separated from the clot via centrifugation, and stored at
–20°C until it is analyzed for cytokine concentrations.

Following blood collection, the rats are euthanized, and their skins removed. Tissue samples (4 from each site) from both the treated site and contralateral site (untreated) are obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial, and flash frozen in liquid nitrogen. The frozen tissue sample is then suspended in 1.0 mL RPMI medium (Celox, Hopkins, MN) containing 10% fetal bovine serum (Sigma, St. Louis, MO), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue is homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, OK) for approximately 1 minute. The tissue suspension is then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris. The supernatant is collected and stored at –20°C until analyzed for cytokine concentrations.

ELISAs for rat MCP-1 are purchased from BioSource Intl. (Camarillo, CA) and rat TNF-α are purchased from BD Pharmingen (San Diego, CA) and performed according to manufacturer's specifications. Results are expressed in pg/ml, the values for the tissue samples are normalized per 200 mg of tissue. The sensitivity of the MCP-1 ELISA is 12 pg/ml and the sensitivity of the TNF-α ELISA is 31 pg/ml.

Table 18

Cytokine Induction										
IRM Cream Treated Animals							Normal Animals			
Cream of Example	MCP-1 (pg/ml)			TNF-α (pg/ml)			MCP-1 (pg/ml)		TNF-α (pg/ml)	
	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Tissue	Serum	Tissue
136	119	1208	51	64	808	85	73	39	64	67
137	90	1815	78	78	597	78	73	39	64	67
138	5	1351	27	66	636	69	73	39	64	67
139	62	1509	85	50	443	75	73	39	64	67
140	24	2373	28	80	948	95	73	39	64	67

What is Claimed is:

1. A pharmaceutical formulation comprising:
an immune response modifier (IRM) compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2- bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;

a fatty acid;

a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and

a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

2. The formulation according to claim 1 wherein the formulation further comprises a preservative system and an emulsifier.

3. The formulation according to claim 1 wherein the hydrophobic, aprotic component has a hydrophilic lipophilic balance of less than 2.

4. The formulation according to claim 1 wherein the hydrophobic, aprotic component has a pKa greater than 14.2.

5. The formulation according to claim 1 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

6.. The formulation according to claim 1 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

7. The formulation according to claim 1 wherein the fatty acid is isostearic acid.

8. The formulation according to claim 1 wherein the hydrophobic, aprotic component is selected from aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

9. The formulation according to claim 8 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or a combination thereof.

10. The formulation according to claim 8 wherein the hydrocarbon of 8 or more carbon atoms is mineral oil or petrolatum.

11. The formulation according to claim 1 wherein the hydrophilic viscosity enhancing agent comprises a carbomer.

12. The formulation according to claim 2 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

13. The formulation according to claim 2 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

14. The formulation according to claim 2 wherein the preservative system comprises iodopropynyl butylcarbamate.

15. The formulation according to claim 2 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

16. The formulation according to claim 2 wherein the preservative system

comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

17. The formulation according to claim 2 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

18. The formulation according to claim 2 wherein the preservative system comprises a preservative enhancing solubilizer.

19. The formulation according to claim 18 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

20. The formulation of claim 2 comprising:

(a) 0.001 to 5% w/w

2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*] [1,5]naphthyridin-4-amine,
N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,
1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
2-butyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,8]naphthyridin-4-amine,
1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
2-methylthiazolo[4,5-*c*]quinolin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
2-ethylthiazolo[4,5-*c*]quinolin-4-amine,
4-amino-2-butyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine-1-ethanol,
1-{2-[3-(3-pyridyl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
1-(2-phenoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
1-[(R)-1-phenylethyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
1-[2-(pyridin-4-ylmethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine,

N-[3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl] cyclohexanecarboxamide,
2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl} ethanesulfonamide,
N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl} propanamide,
1-[2-(methylsulfonyl)ethyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
2-ethyl-1-[4-(ethylsulfonyl)butyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
N-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl} cyclopentanecarboxamide,
1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine,
4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol,
2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine,
or a combination thereof;

(b) 0.05 to 40% w/w isostearic acid;
(c) 1 to 30% w/w hydrophobic, aprotic component;
(d) 0.5 to 10% w/w emulsifier;
(e) 0.01 to 30% w/w preservative system; and
(f) 0.1 to 10% carbomer.

21. The formulation of claim 20 comprising:

(a) 0.03 to 3% w/w 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea, 2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine,or a combination thereof;

(b) 3 to 25% w/w isostearic acid;
(c) 3 to 15% w/w hydrophobic, aprotic component;
(d) 0.75 to 3.5% w/w emulsifier;
(e) 0.1 to 25% w/w preservative system; and
(f) 0.5 to 5% w/w carbomer.

22. A method of treating a dermal associated condition, the method comprising a step of: applying to skin a formulation comprising an immune response modifier (IRM) selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

23. The method according to claim 22 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

24. The method according to claim 22 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

25. The method according to claim 22 wherein the hydrophobic, aprotic component is selected from the group consisting of aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

26. The method according to claim 25 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

27. The method according to claim 22 wherein the hydrophilic viscosity enhancing agent comprises a carbomer.

28. The method according to claim 22 wherein the topical formulation further comprises:

a preservative system; and

an emulsifier.

29. The method according to claim 22 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c] [1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-methylthiazolo[4,5-c]quinolin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethylthiazolo[4,5-c]quinolin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,

1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine,

N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl] cyclohexanecarboxamide,

2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl} ethanesulfonamide,
N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl} propanamide,
1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c]quinolin-4-amine,
2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine,
2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c]quinolin-4-amine,
N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl} cyclopentanecarboxamide,
1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,
8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-c]quinolin-6-amine,
4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol,
2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

30. The method according to claim 22 wherein the dermal associated condition is selected from actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

31. The method according to claim 30 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c] [1,5]naphthyridin-4-amine,
N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,
1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine,
2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,
1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-methylthiazolo[4,5-c]quinolin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-ethylthiazolo[4,5-c]quinolin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,
1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,
1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine,
N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl] cyclohexanecarboxamide,
2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,
N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl} ethanesulfonamide,
N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl} propanamide,
1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c]quinolin-4-amine,
2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine,
2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c]quinolin-4-amine,
N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl} cyclopentanecarboxamide,
1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,
8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-c]quinolin-6-amine,
4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol,
2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

32. The method according to claim 30 wherein the formulation further comprises a preservative system and an emulsifier.

33. The method according to claim 32 wherein the preservative system comprises

methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

34. The method according to claim 32 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

35. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate.

36. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

37. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

38. The method according to claim 32 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

39. The method according to claim 32 wherein the preservative system comprises a preservative enhancing solubilizer.

40. The method according to claim 39 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

41. A method for delivering an immune response modifier (IRM) to a dermal surface, the method comprising the steps of:

selecting a formulation comprising:

(a) an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2- bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;

(b) a fatty acid;

(c) a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and

(d) a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers; and

applying the selected topical formulation to the dermal surface.

42. A pharmaceutical formulation comprising:
an immune response modifier (IRM) compound selected from the group consisting of imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, and thiazolonaphthyridine amines;
a fatty acid; and
a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

43. The formulation according to claim 42 wherein the formulation further comprises a preservative system.

44. The formulation according to claim 42 wherein the hydrophobic, aprotic component has a hydrophilic lipophilic balance of less than 2.

45. The formulation according to claim 42 wherein the hydrophobic, aprotic

component has a pKa greater than 14.2.

46. The formulation according to claim 42 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

47. The formulation according to claim 42 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

48. The formulation according to claim 42 wherein the fatty acid is isostearic acid.

49. The formulation according to claim 42 wherein the hydrophobic, aprotic component is selected from aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

50. The formulation according to claim 49 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

51. The formulation of claim 49 wherein the hydrocarbon of 8 or more carbon atoms is mineral oil or petrolatum.

52. The formulation according to claim 43 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

53. The formulation according to claim 43 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

54. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate.

55. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

56. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

57. The formulation according to claim 43 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

58. The formulation according to claim 43 wherein the preservative system comprises a preservative enhancing solubilizer.

59. The formulation according to claim 58 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

60. The formulation of claim 43 comprising:

(a) 0.001 to 5% w/w imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, thiazolonaphthyridine amine, or a combination thereof;

(b) 0.05 to 40% w/w isostearic acid;

(c) 1 to 30% w/w hydrophobic, aprotic component; and

(d) 0.01 to 30% w/w preservative system.

61. The formulation of claim 43 further comprising an emulsifier and a hydrophilic viscosity enhancing agent.

62. The formulation of claim 60 further comprising an emulsifier and a hydrophilic viscosity enhancing agent.

63. The formulation of claim 62 wherein the viscosity enhancing agent comprises a carbomer.

64. The formulation of claim 63 comprising:

(a) 0.03 to 3% w/w

2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c] [1,5]naphthyridin-4-amine,
N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,
2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,
1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,
1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
or a combination thereof;

(b) 3 to 25% w/w isostearic acid;
(c) 3 to 15% w/w hydrophobic, aprotic component;
(d) 0.1 to 25% w/w preservative system;
(e) 0.75 to 3.5% w/w emulsifier; and
(f) 0.5 to 5% w/w carbomer.

65. A method of treating a dermal associated condition, the method comprising a step of: applying to skin a formulation comprising an immune response modifier (IRM) chosen from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

66. The method according to claim 65 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

67. The method according to claim 65 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

68. The method according to claim 65 wherein the hydrophobic, aprotic component is selected from the group consisting of aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

69. The method according to claim 68 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

70. The method according to claim 65 wherein the formulation further comprises:

a preservative system; and
an emulsifier.

71. The method according to claim 65 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c] [1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,
2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,
1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,
1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

72. The method according to claim 65 wherein the dermal associated condition is actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

73. The method according to claim 72 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c] [1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,
2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,
1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,
1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,
2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

74. The method according to claim 72 wherein the formulation further comprises: a
preservative system; and
an emulsifier.

75. The method according to claim 74 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

76. The method according to claim 74 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

77. The method according to claim 74 wherein the preservative system comprises iodopropynyl butylcarbamate.

78. The method according to claim 74 wherein the preservative system

comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

79. The method according to claim 74 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

80. The method according to claim 74 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

81. The method according to claim 74 wherein the preservative system comprises a preservative enhancing solubilizer.

82. The method according to claim 81 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

83. A method for delivering an immune response modifier (IRM) to a dermal surface, the method comprising the steps of:

selecting a formulation comprising:

- (a) an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;
- (b) at fatty acid;
- (c) a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and

applying the selected formulation to the dermal surface.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/38190

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4745 A61K31/4375 A61K31/4355 A61K31/4365 A61K31/437
A61K47/00 A61K47/26 A61K47/36 A61K47/38 A61K47/44
A61P17/00 A61P17/02 A61P17/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOLLET J L ET AL: "DEVELOPMENT OF A TOPICALLY ACTIVE IMIQUIMOD FORMULATION" PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY, NEW YORK, NY, US, vol. 4, no. 1, January 1999 (1999-01), pages 35-43, XP000900717 ISSN: 1083-7450 abstract page 36, column 1, paragraphs 3,4 page 40, column 2 -page 41, column 2, paragraph 2 page 42, column 2, paragraph 4 -page 43, paragraph 2 --- -/--	1-3,7,8, 10-12, 18,22, 25, 27-29,41

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search 22 April 2003	Date of mailing of the international search report 07/05/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Houyvet, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 40228 A (3M INNOVATIVE PROPERTIES CO) 13 July 2000 (2000-07-13) page 1, line 5-15 page 1, line 23 -page 2, line 7 page 4, line 10-15 page 5, line 5 -page 27, line 15 page 28, line 9 -page 31, line 2	1-83
Y	US 5 238 944 A (BERGE STEPHEN M ET AL) 24 August 1993 (1993-08-24) cited in the application column 1, paragraphs 8,9 column 2, paragraphs 1,2 column 3, paragraphs 3,4 column 4, paragraphs 3-11 example 10	1-83
Y	US 6 110 929 A (MARSZALEK GREGORY J ET AL) 29 August 2000 (2000-08-29) column 1, paragraph 2 column 6, paragraph 5 -column 7, paragraph 1 column 13, paragraph 3 column 14, paragraphs 3,4	1-83
Y	MILLER R L ET AL: "IMIQUIMOD APPLIED TOPICALLY: A NOVEL IMMUNE RESPONSE MODIFIER AND NEW CLASS OF DRUG" INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, ELMSFORD,NY, US, vol. 21, no. 1, January 1999 (1999-01), pages 1-14, XP000900725 ISSN: 0192-0561 abstract page 10	1-83
Y	US 4 595 586 A (FLOM MERLYN G) 17 June 1986 (1986-06-17) column 2, paragraph 2; example 2	1-83
Y	US 4 800 076 A (LUKENBACH ELVIN R ET AL) 24 January 1989 (1989-01-24) column 1, paragraph 10 -column 2, paragraph 2	1-83
P,Y	WO 02 46188 A (3M INNOVATIVE PROPERTIES CO ;MERRILL BRYON A (US); CROOKS STEPHEN) 13 June 2002 (2002-06-13) page 3, line 5 -page 7, line 10 page 26, line 9 -page 27, line 10	1-83

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/38190

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 22-41 and 65-83 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Interna[illegible]l Application No
PCT/US 02/38190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0040228 A	13-07-2000	AU 2721600 A	24-07-2000
		BR 0007435 A	04-12-2001
		CA 2361936 A1	13-07-2000
		CZ 20012446 A3	16-01-2002
		EP 1140091 A2	10-10-2001
		HU 0200329 A2	29-07-2002
		JP 2002534377 T	15-10-2002
		NO 20013230 A	10-09-2001
		PL 349773 A1	09-09-2002
		SK 9542001 A3	03-12-2001
		TR 200101943 T2	22-04-2002
		WO 0040228 A2	13-07-2000
		US 2003045543 A1	06-03-2003
		US 2002058674 A1	16-05-2002
US 5238944 A	24-08-1993	AU 631585 B2	03-12-1992
		AU 4670689 A	21-06-1990
		CA 2004597 A1	15-06-1990
		DE 68911499 D1	27-01-1994
		DE 68911499 T2	30-06-1994
		DK 613889 A	16-06-1990
		EP 0376534 A1	04-07-1990
		ES 2062043 T3	16-12-1994
		HK 1006275 A1	19-02-1999
		IE 62569 B1	08-02-1995
		IL 92537 A	12-04-1994
		JP 2282327 A	19-11-1990
		JP 2915034 B2	05-07-1999
		KR 150445 B1	15-10-1998
		NZ 231655 A	25-06-1992
		US 5736553 A	07-04-1998
		ZA 8909450 A	26-09-1990
US 6110929 A	29-08-2000	AU 748050 B2	30-05-2002
		AU 5133199 A	21-02-2000
		BR 9912448 A	09-10-2001
		CA 2338504 A1	10-02-2000
		CN 1320126 T	31-10-2001
		CZ 20010327 A3	15-08-2001
		EP 1100802 A1	23-05-2001
		HU 0103137 A2	28-01-2002
		JP 2002524392 T	06-08-2002
		NO 20010497 A	27-03-2001
		PL 347590 A1	08-04-2002
		SK 1402001 A3	06-08-2001
		TR 200100278 T2	21-08-2001
		WO 0006577 A1	10-02-2000
		US 2003065006 A1	03-04-2003
		US 2003045545 A1	06-03-2003
		US 2003064968 A1	03-04-2003
		US 6323200 B1	27-11-2001
		US 2002072528 A1	13-06-2002
US 4595586 A	17-06-1986	AU 579458 B2	24-11-1988
		AU 5499686 A	12-03-1987
		JP 62051608 A	06-03-1987
		KR 8902021 B1	08-06-1989
		NZ 215561 A	24-02-1989

INTERNATIONAL SEARCH REPORT

Interna[illegible]al Application No
PCT/US 02/38190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4800076 A	24-01-1989	AU 611131 B2	06-06-1991
		AU 1305588 A	15-09-1988
		BR 8801105 A	18-10-1988
		CA 1306953 A1	01-09-1992
		ES 2009187 A6	01-09-1989
		GR 88100152 A ,B	31-01-1989
		IE 61761 B1	30-11-1994
		IT 1219857 B	24-05-1990
		JP 63243015 A	07-10-1988
		KR 9616196 B1	06-12-1996
		NO 881113 A ,B,	14-09-1988
		NZ 223705 A	27-03-1990
		PH 24775 A	30-10-1990
		PT 86946 A ,B	01-04-1988
		SE 503137 C2	01-04-1996
		SE 8800786 A	14-09-1988
		ZA 8801780 A	29-11-1989
WO 0246188 A	13-06-2002	AU 3061802 A	18-06-2002
		AU 3248202 A	18-06-2002
		AU 3249702 A	18-06-2002
		AU 3951602 A	18-06-2002
		AU 3951702 A	18-06-2002
		AU 3953002 A	18-06-2002
		WO 0246188 A2	13-06-2002
		WO 0246189 A2	13-06-2002
		WO 0246190 A2	13-06-2002
		WO 0246191 A2	13-06-2002
		WO 0246192 A2	13-06-2002
		WO 0246193 A2	13-06-2002
		US 2003065005 A1	03-04-2003
		US 2002193396 A1	19-12-2002
		US 2002173655 A1	21-11-2002